2019

The effects of dopamine and dopamine precursor medication on impairments to high-level vision in Parkinson's disease

Stephen Jon Anderson
Iowa State University

The effects of dopamine and dopamine precursor medication on impairments to high-level vision in Parkinson's disease

by

Stephen Anderson

A dissertation proposal submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Co-majors: Cognitive Psychology; Neuroscience

Program of Study Committee:
Eric Cooper, Co-major Professor
Elizabeth Stegemöller, Co-major Professor
Shana Carpenter
Veronica Dark
Ann Smiley-Oyen

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University

Ames, Iowa

2019

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

ABSTRACT

The goal of this study was to examine how dopamine (DA) and dopaminergic medications affect the performance of high-level visual tasks in individuals with Parkinson's disease (PD). Various studies have reported that PD is associated with impairments on visual tasks known to depend on processing in the ventral visual pathway of the brain. Because most behavioral symptoms in PD arise from chronic dopamine deficiency, the author sought to investigate the role that DA played in cognitive vision. Accordingly, five complex visual tasks were chosen that were known to recruit processing from different constellations of brain areas, either in the ventral pathway or to which the ventral pathway was known to send projections. The tasks included discrimination of abstract objects and three-dimensional face stimuli, visual working memory for these same stimuli, and mental rotation of three-dimensional wire-frame objects. An additional task, in which participants were required to discriminate between pairs of lines with varying orientations, was included as a control. Individuals with PD, as well as healthy age- and sex-matched control participants, completed all five of these tasks twice, and individuals with PD, in particular, were asked to complete them once on and once off of their prescribed dopaminergic medications.

The PD group performed significantly worse than the group of healthy control participants across all five tasks. Strikingly, the performance of individuals in the PD group did not differ significantly depending on their medication state. This finding indicates either that dopamine deficiency is not responsible for cognitive visual impairments in PD, or that the dopaminergic circuitry responsible for these impairments is incapable of responding to the administration of dopaminergic medication. Further, since all tasks, including the line orientation discrimination task, showed an effect of group, the results of this study are insufficient to rule out the possibility that impairments that have been reported elsewhere as cognitive visual deficits in PD are simply the result of deficits in more basic visual processing. Finally, the results of this study provide preliminary evidence that impairments of mental

rotation in PD are the result of impaired processing in brain regions traditionally associated with motor functioning.

CHAPTER 1. BACKGROUND

1.1 General Introduction

While Parkinson's disease (PD) is most commonly associated with deficits in motor functioning, in many cases it is also characterized by a variety of deficits in cognition and perception. Specifically, a broad spectrum of visual symptoms has been observed in individuals diagnosed with PD, ranging from impairments in low-level vision (e.g., deficits in visual acuity and contrast sensitivity) to difficulty with relatively high-level visual processing (e.g., object recognition and mental object manipulation). The focus of this study is on symptoms that emerge from altered processing in the ventral cortical visual pathway and how these symptoms respond to PD treatment using dopamine precursor drugs.

Many of the signature effects of PD result from the death of dopaminergic neurons in the substantia nigra pars compacta, a structure in the basal ganglia (BG). The pathology in these neurons produces a profound dopamine (DA) deficiency in the areas to which they project. However, it has been established that dopaminergic signaling in other parts of the brain is also altered in PD, with some of these areas displaying disease markers similar to those observed in the substantia nigra pars compacta (e.g., dopaminergic cell death and deposits of misfolded α-synuclein). The fact that DA receptors have been discovered in a variety of regions throughout the human visual system thus lends credence to the view that abnormal dopaminergic transmission could be responsible for the impairments that individuals with PD display on visual tasks. Additionally, several pathways have been identified that strongly connect areas of the ventral visual pathway with structures in the BG that are known to exhibit DA deficiency in individuals with PD. There are thus a series of neural mechanisms by which disruption of DA activity in the brain could adversely affect higher vision in individuals with PD.

This study was designed to investigate the hypothesis that disruptions in complex object recognition that occur in PD are the result of abnormal dopaminergic signaling in the ventral visual pathway. In support of this project, there were two specific aims. The first was to determine the extent

to which performance of ventral pathway-dependent visual tasks varies between ON-meds and OFF-meds states. The second was to use any observed performance differences between individuals with PD and their healthy counterparts to determine the location in the brain where visual processing might be breaking down. Accordingly, five experiments were designed to assess cognitive vision that recruits processing resources at various levels of this pathway. In designing the experimental tasks, consideration was also given to assessing visual abilities that would be important in an individual's activities of daily living.

Experiment 1 consisted of a line orientation discrimination task in which participants were presented with pairs of lines and asked to indicate whether the orientations of the two lines were the same or different. Experiment 2 consisted of object and face discrimination tasks in which participants were asked to indicate whether two simultaneously presented three-dimensional stimuli were the same or different. Experiment 3 consisted of a visual working memory task in which participants were presented with face and object stimuli similar to those used in Experiments 2a and b and asked to remember them for a short duration once the objects disappeared from the monitor. A face or object (from the same category as the previously studied stimuli) subsequently appear on the screen and the participants were asked to indicate whether that stimulus was the same as or different from the previously studied stimulus. Experiment 5 consisted of a mental rotation task in which participants were simultaneously presented with two wire-frame objects either at the same perspective or rotated in depth and asked to indicate whether they were the same or different.

Participants in these experiments included 14 individuals diagnosed with idiopathic PD who were on a stable regimen of levodopa (a DA precursor medication) and 14 age- and sex-matched controls. To measure the effects of DA on visual processing, participants in the PD group performed each of the five visual tasks both on and off medication. Based on previous literature, the author expected that participants would perform all tasks better while taking their normally prescribed dosages

of medication, while allowing that the improvement may be larger or smaller depending on the task. A pilot study was conducted in which participants completed a task that aggregated the five tasks above into a single, more complex visual task, and performance was compared between individuals with PD taking their normal medication and healthy control participants of similar age. Though there was appreciably more variability in scores for the PD group, the group as a whole scored significantly lower than the group of healthy individuals on the task.

1.2 Dopamine

Dopamine is the most prominent of a class neurotransmitters referred to as catecholamines, a class of molecules characterized by their incorporation of a benzene ring with two adjacent hydroxyl groups (Missale et al., 1998). DA is synthesized from tyrosine, an amino acid commonly consumed in a normal diet or produced by the conversion of phenylalanine by enzymes in the liver and within DA neurons (Elsworth & Roth, 1997). Under normal circumstances, DA synthesis proceeds by uptake of tyrosine into DA neurons through a series of transport processes, whereupon it is converted into dihydroxyphenylalanine (L-DOPA or levodopa) by the enzyme tyrosine hydroxylase (Elsworth & Roth, 1997). Importantly, conversion of tyrosine to levodopa is typically the rate-limiting step in DA synthesis, meaning that under normal circumstances it is less effective to increase DA levels *in vivo* by increasing tyrosine than by increasing its downstream products (Elsworth & Roth, 1997). The subsequent conversion of levodopa into DA is accomplished through the action of an enzyme called aromatic amino acid decarboxylase. In the human brain, DA is produced primarily in two areas: the substantia nigra pars compacta of the BG and the ventral tegmental area of the midbrain (Vitay & Hamker, 2007). From these two areas, DA follows multiple pathways to diverse areas of the brain; both cortical (e.g., the medial prefrontal cortex) and subcortical (e.g., the thalamus and superior colliculus of the midbrain).

The receptors for DA in the central nervous system are a group of metabotropic G protein-coupled receptors. There are currently five recognized subtypes of DA receptors (D_1 to D_5) that are

differentiated on the basis of their DNA sequences and pharmacological properties (Missale et al., 1998). Some classifications also differentiate between D_{2short} and D_{2long}, which are splice variants of the D_2 receptor with no known differences in their pharmacological profile (Elsworth & Roth, 1997; Missale et al., 1998). For convenience, this taxonomy of receptor subtypes is often broken down D_1-type (i.e., D_1 and D_5) and D_2-type (i.e., D_2 to D_4) on the basis of their downstream effects on adenylyl cyclase (Missale et al., 1998). Adenylyl cyclase is a membrane-bound protein that catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate (Sunahara et al., 1996). Cyclic adenosine monophasphate, in turn, is an intracellular signaling molecule that functions, among other things, to activate protein kinase A, which plays a role in releasing intracellular calcium stores and opening calcium channels in the cell membrane (Missale et al., 1998). Activation of D_1-type receptors has the effect of increasing the activity of adenylyl cyclase, while D_2-type receptors tend to decrease the activity of adenylyl cyclase. D_2-type receptors have also been shown to increase cell hyperpolarization by facilitating potassium efflux from the cell (Missale et al., 1998).

Understanding the physiology and distribution of DA receptors is essential for understanding the symptoms that result when DA-dependent circuitry in the brain is damaged. The next section explores the pathology of PD and how it arises from chronic DA depletion.

1.3 Parkinson's Disease

Much of the pathology of PD is attributed to the death of DA-producing neurons in the substantia nigra pars compacta (Gurevich & Gurevich, 2010). The result is a chronic DA deficiency in the striatum, as well as other areas of the brain that depend on DA synthesized in the substantia nigra pars compacta. The resulting motor symptoms are largely a complex product of dysfunction in the BG circuitry (though some symptoms, like resting tremor, have a more complex pathology) (Brichta, Greengard, & Flajolet, 2013; Gurevich & Gurevich, 2010). The rate model, which is still featured in many textbook descriptions of PD, characterizes this dysfunction as an imbalance of excitatory and inhibitory

activity between regions in the BG. The striatum (composed of the caudate and putamen) is the primary input structure for the BG, receiving inputs from virtually every region of the cerebral cortex and a variety of subcortical structures (Gerfen & Surmeier, 2011). These inputs to the striatum are principally glutamatergic. Glutamate is a neurotransmitter that has an excitatory effect on the spiny projection neurons that comprise about 90% of striatal neurons. DA plays a modulatory role on this glutamatergic input, either increasing or decreasing its excitatory influence depending on the whether it binds to D_1 or D_2 receptor subtypes (Gurevich & Gurevich, 2010). These two receptor subtypes are segregated in spiny projection neurons forming two pathways through the BG: D_1 receptors are expressed exclusively by spiny projection neurons in the direct pathway, while D_2 receptors are expressed exclusively by spiny projection neurons in the indirect pathway. The output structures of the BG (the globus pallidus internal segment and the substantia nigra pars reticulata) tonically inhibit neurons in the thalamus, and the direct and indirect pathways produce opposing effects on this inhibitory influence; activity in the direct pathway decreases thalamic inhibition, and activity in the indirect pathway increases thalamic inhibition. According to the rate model, when dopaminergic neurons of the substantia nigra pars compacta die, the resulting DA deficiency in the striatum produces an imbalance in the activity of the direct and indirect pathways favoring the indirect pathway, which in turn results in an increase in inhibitory input to the thalamus (Gurevich & Gurevich, 2010).

In contrast to the rate model, more recent research has attributed motor symptoms in PD to abnormal patterns of synchronization within the BG and focused on dopaminergic inputs to the subthalamic nucleus instead of the striatum. In this model, a critical role for DA in healthy individuals is acting on the subthalamic nucleus to prevent the development of hypersynchronous activity between the subthalamic nucleus, globus pallidus internal segment, and globus pallidus external segment (Wilson & Bevan, 2011). PD has been associated with buildups of such activity, with synchronicity in different frequency bands associated with particular parkinsonian symptoms. Brown and colleagues (2001) have

shown that individuals with PD who have withdrawn from their antiparkinsonian medications develop characteristic patterns of hypersynchronous activity in the theta and beta bands that is predictive of abnormal motor activity. This abnormal activity and the corresponding symptoms subside when these individuals resume taking their medications.

Irrespective of the underlying mechanisms, the resulting motor symptoms include (but are not limited to): bradykinesia, resting tremor, muscle rigidity, postural instability, and changes in gait (Gurevich & Gurevich, 2010; Brichta, Greengard, & Flajolet, 2013). Patients with PD may also experience a variety of non-motor symptoms, including autonomic dysfunction, gastrointestinal dysfunction, and sleep disorders. Individuals may also experience a spectrum of cognitive symptoms, including anxiety, depression, memory impairment, hallucinations, dementia, and generalized cognitive decline.

The BG has fairly robust mechanisms to compensate for the loss of DA. In a healthy brain, the BG possesses an excess population of dopaminergic neurons in the substantia nigra pars compacta, so the death of these neurons may go largely unnoticed in the initial stages of PD (Elsworth & Roth, 1997). Additionally, dopaminergic neurons that are initially spared can upregulate their synthesis of DA to partially compensate for the death of other neurons. It has also been observed that the substantia nigra pars compacta can further compensate for the loss of endogenous DA by downregulating the number of DA reuptake sites, which allows the remaining DA to be used to greater effect in synaptic transmission (Elsworth & Roth, 1997). Finally, research has indicated that D_1 and D_2 receptors in the striatum are upregulated in PD. As a result of these various compensatory mechanisms, symptoms of DA depletion in the BG are not likely to be observed in the early stages of pathology or injury. In the case of parkinsonism, motor symptoms may not be observed until overall levels of striatal DA fall to near 20% of their initial values (Elsworth & Roth, 1997).

1.4 Dopaminergic Medication in PD

The primary goal of drug therapy in PD is simply to restore DA to its normal levels by replacing it either with DA itself or molecules that mimic its effects (Elsworth & Roth, 1997). Accordingly, a number of medications have been developed that fall under the categories of either DA agonists (i.e., molecules that are not chemically identical to DA, but which possess similar binding properties) or DA precursors (i.e., molecules that can be made into DA by an individual's own mechanisms for DA synthesis).

1.4.1 DA Agonist Medication

Agonist medications are used to treat symptoms of PD by mimicking the effects of DA at receptors that lack sufficient endogenous DA to function properly (Elsworth & Roth, 1997; Gurevich & Gurevich, 2010). Instead of simply replenishing the brain's supply of biologically available DA, the pharmacological profiles of agonists can be manipulated to target specific symptoms of PD or optimize the drug's time course (Gurevich & Gurevich, 2010).

Agonist molecules can be engineered to selectively target the activity of specific classes of DA receptors, binding preferentially to D_1, D_2, or D_3 receptors, or some combination of these (Gurevich & Gurevich, 2010). For instance, peroglide (trade names Permax, Prascend) functions as an agonist for D1 and D2 receptors, while pramipexole (trade names Mirapex, Mirapexin, and Sifrol) functions as an agonist for D2 and D3 receptors. The ability to bind to these receptor subtypes with differing affinities is useful because different subtypes are associated with different symptoms in PD. For instance, while most of the motor symptoms in PD are associated with DA deficiency at D_1 and D_2 receptors, D_3 receptors have been implicated in several of the non-motor symptoms, including depression (Brichta, Greengard & Flajolet, 2013; Gurevich & Gurevich, 2010). Currently, most (if not all) FDA-approved agonist medications are D_2/D_3 selective (Brichta, Greengard & Flajolet, 2013).

Additionally, agonist medications have been developed that remain at therapeutic concentrations in the bloodstream for significantly longer than either earlier agonist medications or

precursor medications. For example, cabergolide (trade name Dostinex) has a half-life of 76-100hrs (Gurevich & Gurevich, 2010). This is desirable feature because the dosage curves associated with shorter-lived drugs produce blood concentrations that are phasic and continuously variable. This phasic DA activity is thought to be a major cause of dyskinesias (i.e., patterns of involuntary, purposeless movements).

There are, however, several disadvantages of using DA agonist medications to treat the symptoms of PD. First, while short-lived agonists are implicated in the onset of dyskinesias, longer-lived agonists, which provide relatively continuous DA stimulation, are more likely to induce tolerance effects (Gurevich & Gurevich, 2010). This is particularly common in D_1-selective agonists. Further, and perhaps more problematically, dopaminergic stimulation resulting from agonist medications occurs independently of the neural activity that normally triggers DA release (Gurevich & Gurevich, 2010; Szczypka et al., 1999). In a healthy brain, DA is released via exocytosis from a presynaptic neuron in response to the summed activity of inputs to that neuron. DA release in this context thus carries information about upstream neural activity that is subsequently conveyed to the postsynaptic neuron. However, DA agonists simply persist in the extracellular space until they are bound by a target DA receptor, so their presence is not indicative of activity in the presynaptic neuron. This means that while DA agonists may promote the health of neurons by providing dopaminergic stimulation otherwise absent in individuals with PD, these medications may be less able to support the processing for which these DA-dependent circuits are typically recruited. For instance, researchers have observed that feeding behaviors, which are severely diminished in mice and rats that have lost the ability to produce tyrosine hydroxylase, can be restored through the administration of levodopa (a DA precursor), but not through the administration of DA agonist medication (Szczypka et al., 1999). As a result of these and other considerations, DA agonists are typically only prescribed to patients early in the course of PD to delay the need for precursor medications (Gurevich & Gurevich, 2010).

1.4.2 DA Precursor Medication

The goal of any dopaminergic medication used to treat the symptoms of PD is to replicate the effects of lost DA as closely as possible, ideally with DA. However, administration of DA itself is therapeutically ineffective since molecular DA is polar and thus unable cross the blood-brain barrier. In contrast, levodopa, the only effective DA precursor medication, contains an additional carboxylic acid group (removed by aromatic amino acid decarboxylase in the final step of DA synthesis) that allows it to pass readily through the blood-brain barrier (Elsworth & Roth, 1997). Because the conversion of tyrosine to levodopa is the rate-limiting step in DA synthesis, levodopa is also much more effective than tyrosine in producing symptom relief. A DOPA decarboxylase inhibitor (e.g., carbidopa or benzerazide) is usually co-administered with levodopa to inhibit its conversion to DA prior to crossing the blood-brain barrier (Brichta, Greengard, & Flajolet, 2013; Ball & Lee, 1977).

Because DA is the endogenous ligand for DA receptors, levodopa essentially acts as a non-selective agonist for all receptor subtypes (Gurevich & Gurevich, 2010). Further, because levodopa essentially works to restore the normal process of DA synthesis by removing the constraint of inadequate precursor molecules, the end-product is DA that is packaged into vesicles and released via exocytosis in response to action potentials in the presynaptic neuron. Thus, levodopa acts not only to increase net dopaminergic activity, as DA agonists do, but also acts to preserve the spike-dependent release of DA that may be vital to preserving DA-dependent overt behaviors (Gurevich & Gurevich, 2010; Szczypka et al., 1999).

While some individuals with PD may initially rely on DA agonists to relieve the symptoms of the disease, levodopa is currently the only viable treatment for long-term symptom management (Gurevich & Gurevich, 2010). However, levodopa also has its own limitations. First of all, levodopa is less effective in treating some symptoms than others, with postural instability, and non-motor symptoms less likely to improve (Brichta, Greengard, & Flajolet, 2013). Additionally, while it is extremely effective at treating

symptoms during the early stages of the disease, levodopa becomes less efficacious as increasing numbers of DA-producing cells succumb to the disease. As a result, the dosages required to treat symptoms gradually increase until the symptoms eventually fail to respond. Levodopa is also relatively short-lived in the body, requiring frequent administration. The half-life of levodopa in the blood is actually only approximately 90 minutes, but its effects last appreciably longer because the product DA persists in synaptic vesicles until it is depleted by repeated synaptic activation (Gurevich & Gurevich, 2010). This still means that the time between doses of levodopa is significantly shorter than that necessitated by long-lived DA agonists. Finally, patients eventually develop motor complications, typically between 5 and 7 years after beginning treatment with levodopa (Gurevich & Gurevich, 2010; Brichta, Greengard, & Flajolet, 2013). These include dyskinesias similar to those observed in prolonged treatment with short-lived agonists (though given the formal name levodopa induced dyskinesia (LID) in the case of precursor treatment), which occur in 40-80% individuals with PD.

The differences between these two types of medications have important implications for studying the role of DA in the brain in general, and the visual symptoms in particular. For instance, predicting or interpreting the effects of a DA agonist requires an understanding of which receptor subtypes the agonist is selective for, the distribution of those receptors within brain regions of interest, and myriad pharmacological considerations, such as the binding affinity at each receptor subtype and how this compares to endogenous DA. This interpretation will be further complicated if one is examining behaviors that depend on spike-dependent vesicular release of DA. By contrast, levodopa results in DA that is produced and released by the normal cellular machinery used to produce DA in healthy individuals, making its effects appreciably easier to interpret. All other things being equal, levodopa administration will tend to normalize DA activity in areas where DA is depleted but the receptors and pathways remain relatively intact.

1.5 Visual Symptoms in PD

Though not as commonly associated with the disease as motor deficits, visual deficits frequently occur in individuals with PD. According to a questionnaire study conducted by Urwyler et al. (2014), 77% of individuals with PD report at least one recurring visual symptom, while 43% report two or more. These symptoms can range over the full spectrum of complexity in visual processing, from acuity and contrast sensitivity to visual navigation and face discrimination (Weil et al., 2016). What follows is a list of visual symptoms documented in individuals with PD and a brief description of each. These symptoms are specifically those that could impair processing of stationary objects by individuals with PD who exhibit no symptoms of dementia, so the list is not exhaustive.

1.5.1 Abnormal Visual Evoked Potentials

Visual evoked potentials are the electrical activity that occurs in response to light and pattern stimuli measured at the scalp above the visual cortex. These changes in voltage are used as an indicator of visual pathway function and integrity. Patients with PD exhibit visual evoked potentials with a greater latency than age-matched controls (Bodis-Wollner, 1990; Bodis-Wollner & Yahr, 1978). The delay in visual evoked potentials can be different between the two eyes, and is shortened by administration of levodopa (Bodis-Wollner, 1990), suggesting a role for DA in explaining the electrophysiological variability.

1.5.2 Decreased Visual Acuity

Visual acuity entails the ability to resolve the features of a visual stimulus while controlling for visual contrast (Weil et al., 2016; Jones, Donaldson, & Timmings, 1992). In one study, visual acuity was found to decrease by about 25% in individuals with PD compared to controls, and this deficit showed minimal response to treatment with levodopa (Jones, Donaldson, & Timmings, 1992). However, other studies have shown negligible effects of PD on visual acuity, suggesting instead that dry eyes and

blepharitis (i.e., inflammation of the inner eyelid) were more likely causes of individuals' difficulty with visual acuity tasks (Biousse et al., 2004).

1.5.3 Decreased Contrast Sensitivity (CS)

CS is defined as the ability to discriminate between a coarse object and its background while varying the contrast in brightness between the two (Weil et al., 2016). Because CS can vary across spatial frequencies in somewhat complex ways, it is typically assessed using either letters of varying luminance presented against a white background or using sinusoidal gratings of varying contrast and wavelength (Bodis-Wollner, 1990; Campbell & Maffei, 1974). CS is typically measured as a percentage of luminance of the stimulus compared to the luminance of the background or reference (i.e., 100*(background luminance – stimulus luminance)/background luminance) such that a CS of 50 would indicate that the participant would just be able to detect the change in contrast when the stimulus was half as bright as its background (Regan & Neima, 1984). However, this value is often made more intuitive by stating it as 1/contrast threshold so that higher values indicate greater sensitivity. For example, on some graphs, a CS of 100 indicates that a participant could just detect a difference in contrast of 1/100 the luminance of the background/reference.

Individuals with PD display different CS curves than control participants. In a healthy human adult, the CS curve peaks at spatial frequencies near 4 cycles per degree and falls off progressively at both higher and lower spatial frequencies (Bodis-Wollner, 1990). In contrast, individuals with PD taking dopaminergic medications have curves with generally the same shape, but a significantly reduced CS at the 4 cycles per degree peak. The greatest difference is observed in individuals with PD in the OFF-meds state, for whom the CS curve peaks at 0.5 cycles per degree and falls off progressively at higher spatial frequencies. Put more succinctly, individuals with PD who are not currently taking their medication seem to display an overall decrease in CS compared to healthy controls, but relatively higher CS than

controls at lower spatial frequency. Further, DA medication seems to restore the shape of the curve but not its height.

As with acuity, research has indicated that CS in individuals with PD can vary between the two eyes (Laudate et al., 2013). Research also suggests that CS deficits that accompany PD may be orientation-selective, such that individuals show a greater deficit in CS when sinusoidal gratings are oriented horizontally rather than vertically (Weil et al., 2016).

1.5.4 Spatial Neglect

There have been several reports indicating that some individuals with PD experience visual neglect for the left visual field, but only in cases where they also report that their motor functions are more disrupted on their left side (Weil et al., 2016). For instance, individuals with PD who report left as their most affected side tend to place their mark right of center when instructed to bisect a horizontal line, and tend to disproportionately miss targets presented in the left visual field while performing a line cancellation task (Villardita et al., 1983; Laudate et al., 2013). These individuals may also show delays in making saccades to targets in the left hemifield and spend more time exploring the right side of a visual scene than the left (Weil et al., 2016; Laudate et al., 2013).

1.5.5 Impaired Color Vision

PD has been linked to difficulties in color discrimination. In one study comparing individuals with PD to healthy controls, both groups were given the Farnsworth-Munsell 100 Hue Test (Oh et al., 2010). The results indicated that the PD group performed significantly worse on the 100 Hue Test overall, as well as the subsections specifically examining the red-green and blue-yellow color axes. These impairments were also found to be correlated with severity of motor symptoms. Interestingly, the experimental group in this study represented a fairly broad cross-section of the PD patient population, such that 12 of the 54 individuals had never taken medication for the condition, making the effects of medication on color vision difficult to discern. A variety of other studies have also found impairments in

color discrimination in individuals with PD, though there is conflicting evidence as to whether these individuals tend to show greater impairment on one color axis than the other (or whether there is a difference at all) (Weil et al., 2016). There is also evidence that color vision deficits in PD can be at least partially corrected by administration of levodopa (Büttner et al., 1994).

1.5.6 Impaired Line Orientation Discrimination

Research has demonstrated that individuals with PD may have difficulty discriminating between lines of different orientations (Weil et al., 2016). In multiple studies, PD has been associated with performance on the Judgment of Line Orientation (JLO) test that is significantly lower than the performance of healthy control participants (Montse et al., 2001; Uc et al., 2005). This test requires participants to match each of a pair of target lines to one in an array of 11 reference lines, with adjacent lines in the array separated by 18 degrees (Montse et al., 2001). Interestingly, while participants in the PD group made significantly more errors than control participants overall, the PD group actually made fewer of what the researchers referred to as “mild intraquadrant errors” in which participants confused a target line with one of the reference lines 18 degrees away but in the same quadrant. Deficits in line orientation judgments in PD are associated with duration and severity of the disease (Weil et al., 2016).

1.5.7 Impaired Figure-Ground Discrimination

Though this ability seems to have received less attention than others, PD has been associated with declines in performance on figure-ground discrimination tasks (Weil et al., 2016). Such tasks involve asking participants to identify simple figures embedded in more complex ones. In one study, Flowers and Robertson (1995) used a modified version of the Gottschaldt embedded figure test that allowed researchers to manipulate the complexity of the task, so that on some trials participants were presented with two possible simple figures, only one of which was actually embedded in the complex figure. Both groups were at ceiling on the simpler version of the task, but the PD group scored significantly lower on the more complex version, and scores in the PD group were correlated with age and disease severity

(Flowers & Robertson, 1995). However, other studies have found significant effects of PD on performance of an embedded figure task only in individuals with PD-related dementia and not in other cases (Levin et al., 1991).

1.5.8 Impaired Depth Perception

Individuals with PD are more likely than their healthy counterparts to experience difficulties with stereopsis (Weil et al., 2016). In a study by Kim et al. (2011), 87.5% of drug-naïve PD patients were found to have abnormally low stereopsis according to the Titmus fly test compared to only 10% of control participants. Further, issues with stereopsis in drug-naïve individuals with PD have been correlated with significantly lower scores on a general visual perceptive/construction test (Kim et al., 2011), and loss of grey matter in the right extrastriate visual cortex (Koh et al., 2013). It has also been shown that dysfunction of stereopsis in PD is associated with deficits in color vision, and is not significantly improved by the administration of antiparkinsonian medication (Sun et al., 2014).

In addition to stereopsis, depth perception in humans can also be accomplished through a series of monocular depth cues that do not require disparity of the image between the two retinas. To the best of my knowledge, no studies have examined the effects of PD on depth perception based on monocular cues.

1.5.9 Impaired Object Recognition

Evidence is conflicting regarding the existence of object recognition deficits in PD. While some studies have found patients in intermediate stages of the disease have difficulty identifying overlapping objects (Weil et al., 2016), others have found minimal, if any, deficits in recognizing or identifying non-face objects. A study by Laatu et al. (2004) examined the ability of individuals with PD to perform a broad array of visual object recognition tasks. These tasks ranged from largely visual in nature (e.g., determining whether a figure presented on a screen was a familiar intact object or just a series of scrambled features) to visual tasks with semantic components (e.g., naming an object presented on a

screen, or indicating whether or not an object presented on a screen is an animal). Data for all six tasks were collected from three different groups: cognitively deteriorated patients, cognitively preserved patients, and healthy controls (n = 14 for all groups). Preservation vs. deterioration was defined using the Mild Deterioration battery.

In this study, only two tasks were found where accuracy reliably distinguished the cognitively deteriorated group from the two control groups (Laatu et al., 2004). The first task was the Simple Word Discrimination task, in which participants were asked to press one key when the word “kyllä” (the Finnish word for “yes”) appeared on the screen, or another key when the word “ei” (the Finnish word for “no”) appeared on the screen. The second task was the Object Detection task, in which participants were asked to discriminate between drawings of familiar objects and “scrambled” drawings of those same objects. Differences in error rates between the three groups on all other tasks were non-significant, and interestingly, when the Simple Word Discrimination task was run again on the same sample in the same study, the differences between groups were also non-significant.

1.5.10 Impaired Face Recognition

Studies examining face recognition in persons with PD have found that these individuals may be impaired relative to healthy controls. In a study by Levin et al. (1991), researchers administered a series of visuospatial tasks to both groups and found that the PD group performed significantly worse on the Benton Facial Recognition Test (BFRT). Of the 183 individuals in the PD group, 17 were not taking any sort of antiparkinsonian medication, and another 13 were not taking dopaminergic medications, but were taking anticholinergic medications. However, because these individuals were not analyzed separately, this study did not provide any evidence for the effects of PD medication on task performance. The study did show that PD patients with dementia performed significantly worse on the BFRT than those without dementia. Similar results have also been found by other researchers using the BFRT (Pereira et al., 2009). However, at least one study using an analogous task (subtest 1 of the Florida

Affect Battery-revised failed to find a significant difference in performance between a PD group and a control group discriminating simultaneously presented photographs of faces (Jacobs et al., 1995).

1.5.11 Impaired Facial Expression Recognition

A variety of studies have indicated that individuals with PD may have difficulty interpreting and identifying facial expressions. Jacobs et al. (1995) found that patients with PD generally perform worse than healthy controls at tasks that required them to analyze emotional face imagery. In this study, the researchers found that patients with PD had difficulty determining whether two simultaneously presented faces were expressing the same or different emotions. Patients with PD also performed worse than controls describing facial expressions associated with particular emotions, both when participants were asked to imagine faces with the target expression and when they were actually presented with images of the target emotional expression.

Other studies have found that PD disproportionately impacts perception of negative emotional expressions. These include, but may not be limited to, fear, sadness, and disgust (Weil et al., 2016). Recognition of emotional expression by individuals with PD has been found to improve upon administration of antiparkinsonian medication (Sprengelmeyer et al., 2003).

1.5.12 Impaired Visual Working Memory (VWM)

At least in some instances, PD may be associated with deficits in being able to retain items in VWM. In one study, Pereira et al. (2009) administered Warrington's recognition memory test for faces to both individuals with PD (but not dementia) and healthy control participants to examine their ability to remember novel faces for short durations. Specifically, participants were presented with 50 photographs of novel male faces and asked to rate whether they found these faces pleasant or not. Immediately after participants gave their ratings the same photograph would return to the screen along with a distractor face, and participants were asked to indicate which face they had seen previously.

Analysis revealed that participants with PD scored significantly lower on average on this task than their healthy counterparts

Additionally, DA medication in PD has been shown to play a role in working memory more generally. In a study by Lange et al. (1992), a group of 10 individuals were tested using a series of working memory tasks for which individuals with PD have previously demonstrated significant impairment. In this study, these tasks were administered both while participants were taking their normal dopaminergic medications and following controlled withdrawal. The researchers found that withdrawal from medication tended to exacerbate WM impairments, but did so selectively for WM tasks known to recruit circuits in the frontal lobe.

1.5.13 Impaired Mental Rotation

Several studies have indicated that PD is associated with impairments of mental rotation of objects, though interestingly the exact effect may depend on the axis of rotation. A study by Lee et al. (1998) used a classic set of wire-frame stimuli developed by Shepard and Metzler (1971) to examine the mental rotation abilities of individuals with PD (Lee et al., 1998). Two stimuli were presented simultaneously that were either identical or that varied slightly in one of their components. Additionally, the stimuli could be presented either at the same angle or at angles that differed by between 20 and 180 degrees at increments of 20 degrees. Over the course of two experiments, participants were instructed to indicate whether the two simultaneously presented figures were the same or different, irrespective of the angle between them.

In the first experiment the figures were rotated in depth (i.e., about the vertical axis), and the researchers observed an interaction such that the PD group made significantly more errors than the control group, but only when the stimuli were the same (i.e., when participants falsely identified the stimuli as “different”) (Lee, et al., 1998). Further, the rate of errors by the PD group to stimuli that were the same increased as the angle between them increased, such that when stimuli were rotated more

than 140 degrees with respect to each other, participants actually performed appreciably worse than chance. Specifically, when the stimuli were the same but rotated 180 relative to one another, the error rate for the PD group was approximately 80%. By contrast, in the second experiment the stimuli were rotated in the picture plane. In this case, the PD group produced significantly greater reactions times than the control group, but did not make significantly more errors, irrespective of stimulus type.

Other researchers using different paradigms have failed to observe deficits in mental rotation related to PD. For instance, Ogden, Growdon, and Corkin (1990) presented participants with 2 dimensional shapes and instructed them to indicate which of an array of 3 dimensional objects represented the former shape folded along indicated seams. The error rates for a PD group and a control group were both well above floor, but not significantly different.

Several of the symptoms considered above correspond to visual processes associated with ventral visual pathway function, which is the focus of the present study. The following section contains an examination of the ventral visual pathway and the ways in which its functioning might be affected by the pathology of PD.

1.6 Possible Mechanisms for Visual Symptoms in PD

There are at least three possible avenues by which abnormal DA signaling in the brain could lead to impairments of cognitive vision. First, previously characterized PD pathology in the BG could lead to performance deficits on visual tasks that recruit processing resources from the striatum. Second, PD may lead to impaired dopaminergic signaling in areas of the visual system itself that are required for performance on visual tasks (i.e., without any direct involvement of the BG). Lastly, DA activity within the visual system or other critical areas, which are relatively spared by the effects of PD (at least in the early stages), may be disrupted by the dopaminergic medication used to treat the disease. Each of these possibilities is considered below, along with a fourth possibility that is not subject to the influence of fluctuations in dopaminergic activity.

1.6.1 Model 1: Visual Symptoms May Be Related to Damage in the BG

The striatum in the BG has the highest expression of DA receptor mRNA (both D_1 and D_2) of any region in the human brain (Hurd, Suzuki, & Sedvall, 2001) and dysfunction of dopaminergic signaling in the striatum is believed to be the principal cause of the majority of motor and cognitive deficits in PD (Gurevich & Gurevich, 2010). Thus, to the extent that visual tasks recruit processing resources from the BG, it is likely that the DA depletion in the BG associated with PD would lead to deficits in visual processing. There are several major pathways projecting from the ventral visual pathway to the striatum whose activity might be affected by the pathology of PD in the BG.

The occipitotemporo-neostriatal pathway sends projections from almost every region of the ventral pathway to the striatum of the BG (Kravitz et al., 2013). Moreover, the projections are topographically organized, such that V2 and V4 project to the most caudal regions of the caudate nucleus while progressively more rostral areas of the ventral pathway project to progressively more rostral sites in the caudate tail and the caudoventral putamen. There is potential for information from this pathway to influence processing in myriad areas of the brain through the series of corticostriatal loops that comprise the BG. The areas of the striatum innervated by this pathway also send a projection back to the ventral visual pathway via the substantia nigra pars reticulata and thalamus, providing the opportunity for recurrent processing between the BG and ventral visual pathway (Kravitz et al., 2013; Seger, 2013).

The occipitotemporo-ventral striatum pathway originates entirely from the anterior inferotemporal cortex (IT) and terminates in the ventral striatum, both in the nucleus accumbens and the olfactory tubercle (Kravitz et al., 2013). The ventral striatum, in turn, projects to a variety of cortical and subcortical areas, including lateral prefrontal cortex (PFC), orbitofrontal cortex, amygdala, and hippocampus. This pathway thus provides another opportunity for relatively high-level visual information from the ventral visual pathway to influence processing across diverse areas of the brain.

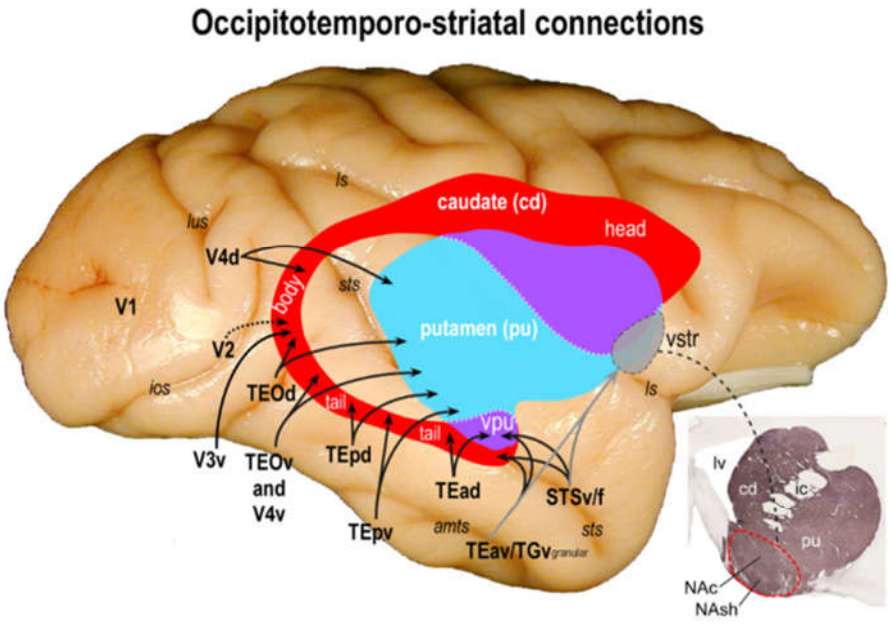


Figure 1. A schematic diagram of connections between the ventral visual pathway and the BG. A number of the BG areas indicated send feedback to the visual pathway by way of the output structures of the BG and several thalamic nuclei. Image from Kravitz et al., 2013.

Given the connectivity between the ventral visual pathway and the BG, it is not surprising that some researchers have at times conjectured that the BG actually subserves high-level visual processing (Middleton & Strick, 1996). Further evidence came from a lesion study by Divac and colleagues (1967), which showed that lesioning of the caudate tail in macaques impaired performance on a visual discrimination task. However, more recent research indicates that these pathways between the BG and the ventral visual pathway are actually involved in more cognitive aspects of processing visual stimuli. Specifically, the occipitotemporo-neostriatal pathway has been implicated in learning visual associations based on reward, such that damage does not lead to impairments in fundamental visual discrimination of stimuli (Fernandez-Ruiz et al., 2001). In contrast, the occipitotemporo-ventral striatum pathway has been implicated in the assignment of value to stimuli (Kravitz et al., 2013). This finding has been supported by imaging studies of humans indicating that the ventral striatum shows selective activation for rewarded outcomes (Liu, X et al., 2011). Given this evidence, PD pathology in the BG seems less likely to disrupt visual object discrimination as such, but would be more likely to disrupt learning of object

associations and values. By extension, supplementing depleted DA in the BG with a DA precursor medication would seem unlikely to improve impaired performance on object discrimination tasks.

1.6.2 Model 2: Visual Symptoms May Be Related to Impaired DA Signaling in the Visual Pathways

DA receptors have been observed in a wide range of visual areas of the human brain. In terms of regions involved in object identification and recognition, these include a variety of areas from the retina (Djamgoz & Wagner, 1992) to regions of the PFC involved in manipulating representations of visual objects (Hurd, Suzuki, & Sedvall, 2001).

In human visual processing, visual information travels from the retina of each eye to V1 (also known as the primary visual cortex or striate cortex) via the lateral geniculate nuclei (LGN) of the thalamus (Callaway, 2005). Studies have shown that the retina (Bodis-Wollner, 1990), as well as the LGN and V1 (Hurd, Suzuki, & Sedvall, 2001), contain dopaminergic circuitry, indicating that DA plays a significant role in very early visual processing.

In the human retina, D2 receptors have been identified in both the inner nuclear layer (containing the cell bodies of the bipolar, horizontal, and amacrine cells) as well as the outer plexiform layer (containing the synapses between the horizontal cells of the inner nuclear layer and the photoreceptors of the outer nuclear layer) (Bodis-Wolner, 1990; Demb & Singer, 2015). DA in the retina is released by amacrine cells and a population of interplexiform cells, and the influence of this DA on the cells of the inner nuclear layer and outer plexiform layer is thought to contribute to light adaptation and establishing the center-surround organization of retinal receptive fields that facilitates edge detection (Bodis-Wollner, 1990; Demb & Singer, 2015). These functions have been proposed as mechanisms by which pathology of the DA circuitry in the retina might lead to loss of CS and delayed visual evoked potentials (Bodis-Wollner, 1990). And, indeed, PD pathology has been observed in the inner retinal layer of the eyes, including misfolded and phosphorylated α-synuclein (Weil et al., 2016). To the best of the

author's knowledge, there has been no research to date characterizing any relationship between the dopaminergic circuitry of the retina and that of the substantia nigra pars compacta.

In a study by Hurd, Suzuki, and Sedvall (2001), researchers used in situ hybridization to examine the distribution of D_1 and D_2 receptor mRNA throughout the entire human brain using whole-hemisphere sections. They found that both receptor subtypes are expressed fairly broadly throughout the brain, with D_2 receptors having higher expression overall, while D_1 receptors had appreciably greater expression in the cerebral cortex. Of more relevance to vision in particular, moderate to high levels of D_2 receptor mRNA were identified in the LGN, while moderate to high levels of D_1 receptor mRNA were identified in the infragranular layers (i.e., layers V and VI) of V1. It would thus be tempting to predict that DA depletion in these areas might lead to deficits in perception of visual features to which the retinal fields of the LGN and V1 are most responsive (e.g., bars of light of particular lengths, either stationary or moving perpendicular to their long axes) (Hubel & Wiesel, 1959). However, the location of DA receptors in the infragranular layers of V1 is particularly striking due to the arrangement of the circuitry between V1 and LGN. Specifically, fibers projecting from the LGN (an area containing relatively high expression of D_2 mRNA) innervate layer IV of V1, but the neurons in layers VI of V1 (i.e., the layer containing relatively high expression of D_1 mRNA) actually project back to the LGN (Cudeiro & Sillito, 2006). Further, the number of corticothalamic fibers projecting from V1 back to the LGN is more than an order of magnitude larger than the feedforward connections between the LGN to V1, such that the corticothalamic projection actually constitutes the single largest input to the LGN. Models of the recurrent processing between these two regions of the brain have predicted that this loop might contribute to visual processes ranging from brightness perception and stereopsis to perception of illusory contours and perceptual grouping (Cudeiro & Sillito, 2006). The state of knowledge concerning the interaction between the LGN and V1 and its functions, as well as precise location and role of DA

receptors in this circuitry, would make any predictions arising from DA depletion and/or replacement in this area speculative at best.

The ventral pathway emerges from V1 and proceeds through the preoccipital gyrus, the inferior temporal gyrus, and the ventral temporal pole (Kravitz et al., 2013). While D_1 and D_2 mRNA is not expressed in these regions at levels that approach those in the BG, the signal from these regions observed by Hurd et al. (2001) was still moderately strong, as it was for much of the cortex. This raises the possibility that dysfunctional DA signaling could lead to deficits in ventral pathway function that could produce deficits in high-level processing similar to those described previously (e.g., face and object recognition, as well as others that depend on processing resources in IT). However, given the broad distribution of DA receptor mRNA in the cortex (disproportionately D_1 mRNA), it is hard to see DA-specific pathology producing visual processing deficits without similarly affecting cortical processing more broadly.

Finally, the ventral pathway sends a projection – known as the occipitotemporo-ventrolateral prefrontal pathway – from anterior aspects of the superior temporal sulcus to the ventrolateral PFC (Kravitz et al., 2013). The ventrolateral PFC is thought to play a significant role in visual processing that recruits working memory functions, and ventrolateral PFC cells in the monkey display strong object selectivity. Damage to this area in monkeys has been shown to lead to deficits in object working memory, while similar damage in humans impairs working memory for faces. These observations make ventrolateral PFC dysfunction a likely source of several of the PD-related visual deficits discussed previously (e.g., performance decrements on mental rotation and VWM tasks). However, the levels of DA receptor mRNA recorded by Hurd et al. in this region were among the lowest recorded anywhere in the cortex. So while these regions may be important for visual object-related tasks requiring working memory, it is not clear what effects, if any, modulation of DA in individuals with PD might have on these tasks.

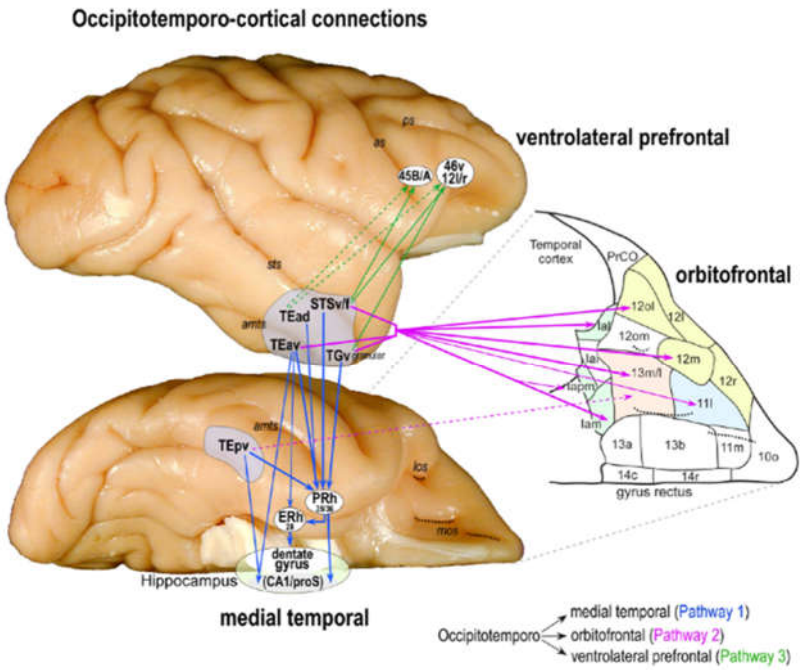


Figure 2. A schematic diagram of the connections between the ventral visual pathway and the frontal cortex. Image from Kravitz et al., 2013.

1.6.3 Model 3: Visual Symptoms May Be Related to Excess DA from DA Precursor Medication

The possibility exists that at least some visual symptoms in PD that are customarily attributed to pathology of the disease itself are actually the result of the medications used to treat it. In a review conducted by Poletti and Bonuccelli (2013), a number of tasks were identified for which performance by PD patients significantly decreased while they were taking their normal levodopa regimen compared to when they were off of their medication. These tasks included probabilistic reversal learning, distractor resistance, probabilistic classification learning, and an episodic memory task. Additionally, patients who took DA agonists instead of levodopa have also displayed performance deficits on cognitive tasks that decreased when they abstained from medication. Specifically, individuals with PD taking pramipexole were shown to perform worse on tasks involving attention, set-shifting, and verbal short-term memory while they were on their medication, and individuals taking apomorphine performed worse on a VWM task while taking their normal medication (Poletti & Bonuccelli, 2013).

In some cases, performance on tasks that initially appear relatively similar can respond in opposing ways to dopaminergic medication in individuals with PD. In one study, patients who had been prescribed levodopa to treat PD were asked to complete two reward-based learning tasks that varied slightly in their learning rules (Graef et al., 2010). In the Instrumental Learning task, reward contingencies remained constant throughout the task such that each stimulus was associated with a particular probability of reward that never changed throughout the task. In the Reversal Learning task, the reward contingencies for each stimulus were changed once a participant reached a criterion of 75% accuracy on the task, requiring the participant to learn a new set of reward contingencies to maximize their performance. Importantly, participants completed each task twice: once while taking their regular prescribed dosage of levodopa, and once after abstaining from the drug for at least 12 hours (treatment orders of drug conditions were counterbalanced to prevent confounding drug and condition order effects). The results showed that participants performed significantly better in instrumental learning task (i.e., under constant reward contingencies) when they were on medication than when they abstained, but participants performed significantly better in the reversal learning task (i.e., under variable reward contingencies) when they were off medication than when they took their prescribed dosage.

One explanation for the inconsistent effects of dopaminergic medication on cognitive task performance is that the loss of DA in the striatum is progressive, beginning in the head of the caudate nucleus and moving caudally over time (Cools, 2006; Poletti & Bonuccelli, 2013). Dopamine depletion in the rostral caudate would initially affect connections between the dorsolateral striatum and the dorsolateral PFC, the dorsomedial globus pallidus, and the thalamus (Poletti & Bonuccelli, 2013). As the loss of DA advanced caudally, it would also affect connections between the ventromedial striatum, the orbitofronto cortex, the dorsomedial globus pallidus, and the thalamus (Poletti & Bonuccelli, 2013). Consistent with this anatomical progression, cognitive tasks relying on reciprocal connectivity between

the BG and the dorsolateral PFC (e.g., task switching,) have been shown to suffer disproportionately early in the course of PD, while those relying on reciprocal connectivity between the BG and orbitofronto cortex (e.g., probabilistic reversal learning) are relatively spared (Cools et al., 2003). Indeed, early cognitive symptoms of PD are often said to resemble those of patients with frontal lobe lesions (Cools et al., 2003; Muslimović et al., 2005). The reason for the detrimental effects of DA on these tasks, is has been suggested, is that dopaminergic medication, while producing therapeutic effects on DA-depleted circuitry, actually has a deleterious effect on the DA circuitry that is spared early in the disease course (Cools, 2006; Poletti & Bonuccelli, 2013). This model is referred to as the "Dopamine Overdose Hypothesis", and predicts that the tasks that are impaired by the administration of dopaminergic medication are those that recruit circuitry that has not yet been compromised by the pathology of PD.

The implications of these studies for the effects of levodopa administration on ventral visual pathway function are unclear. First of all, to the extent that levodopa has been shown to affect vision at all, its effects tend to be either beneficial or negligible. As previously mentioned, abnormal VEP latency (Bodis-Wollner, 1990), as well as deficits in acuity (Jones, Donaldson, & Timmings, 1992), contrast sensitivity (Bodis-Wollner, 1990), color vision (Büttner et al., 1994), stereopsis (Sun et al., 2014), and recognition of facial expressions (Sprengelmeyer et al., 2003) all seem to improve in individuals with PD when they are on dopaminergic medications compared to when they are unmedicated. On the other hand, the contribution of the ventral visual pathway to performance of these visual tasks is likely to be relatively minimal. Abnormalities in visual evoked potentials, acuity, CS, and stereopsis can all potentially be attributed to well-documented pathology of dopaminergic circuits in the retina, while impaired recognition of facial expressions has been attributed by some to pathology in subcortical structures (e.g., the amygdala) (Weil et al., 2016). One possible exception is color vision, which has shown to improve following administration of dopaminergic medication (Büttner et al., 1994). Nonetheless, the effects of levodopa remain to be tested on a variety of visual deficits that can readily

be attributed to ventral visual pathway function, and so it is still an open question as to what effect levodopa will have on these tasks. To the extent than any of these visual symptoms in PD are caused or exacerbated by levodopa administration, withdrawal from levodopa may improve performance on these tasks.

1.6.4 Model 4: Visual Symptoms May Be Related to More General Brain Pathology

While DA depletion is certainly a principal contributor to much of the pathology in PD that affects observable behavior, protein aggregates and cell death also play a role that increases over the course of the disease. It is not entirely clear how much atrophy occurs in the early stages of PD. For instance, Menke et al. (2014) did not observe any significant difference in grey matter volume between a group of cognitively normal individuals with PD and a group of healthy controls using conventional magnetic resonance imaging (MRI) techniques, though a decrease in grey matter was observed using a more sensitive technique known as vertex-wise analysis, which analyzes the shape of subcortical structures. In contrast, a study by Burton et al. (2004) also used MRI and identified significantly decreased grey matter volume in the frontal lobe in a cognitively normal PD group. Another study by Pereira et al. (2009) reported that individuals with PD (but not dementia) showed significantly decreased grey matter in areas of the frontal, temporal and parietal lobes, as well as bilateral cerebellum and limbic structures. For individuals with mild cognitive impairment, decreases in grey matter have also been observed in a variety of cortical areas across the frontal, temporal, and parietal lobes, as well as several subcortical structures (e.g., the amygdala, hippocampus, and right putamen) (Melzer et al., 2011). Those with advanced PD who have developed dementia display more severe losses in grey matter in these areas, but also show decreased volume in other regions, including the posterior cingulate gyrus and the occipital cortex (Melzer et al., 2011; Burton et al., 2004).

Thus, it may be that impairments in ventral pathway-dependent visual processing in individuals with PD occur not because of a partially reversible depletion of DA, but because the circuitry of the

visual pathways has irreversibly broken down. Several studies have reported correlations between visual deficits in PD and decreased grey matter density in specific areas of the brain. For instance, Koh et al. (2013) found that abnormal stereopsis in individuals with PD was associated with significantly reduced grey matter in Brodmann area 18 in the extrastriate visual cortex. Another study by Pereira et al. (2009) tested individuals with PD on their ability to perform Benton's facial recognition test, a visual form discrimination test, and a recognition memory test for faces, and compared participants' scores on these tasks to variations in grey matter density. Decreased performance by individuals with PD on the face recognition task was associated with decreased grey matter volume in the fusiform gyrus, parahippocampus, middle occipital gyrus, and inferior frontal gyrus. In contrast, decreased performance on the visual form discrimination task was associated with grey matter losses in the superior parietal and occipital lobes, as well as in the inferior and middle frontal gyri. Finally, decreased performance on the test of memory for faces was associated with grey matter losses in the right parahippocampus.

In these cases, visual processing deficits in PD may arise simply because the circuitry on which they depend has been destroyed. Even if these circuits once depended on DA for their function, replenishing depleted DA in regions of the brain where dopaminergic circuitry has severely atrophied obviously cannot be expected to provide a meaningful therapeutic effect.

One way to adjudicate among these various possibilities is to examine the effects of DA on visual tasks known to recruit processing from different regions within the ventral visual pathway, as well as regions to which it projects. However, since the experience of individuals with PD withdrawing from their antiparkinsonian medications tends to be unpleasant, it was important to first develop a visual task that could demonstrate performance differences between healthy individuals and individuals with PD. If no such differences existed, or if the task used was incapable of capturing them, it would be ethically dubious to proceed with a study likely to cause appreciable discomfort to participants. The researcher therefore designed and conducted a pilot study comparing the performance of healthy individuals and

individuals with PD in the ON-meds state on a visual task that required multiple perceptual processing steps.

CHAPTER 2: PILOT STUDY

2.1 Design and Justification

The purpose of the current study is to examine the effects of levodopa, a DA precursor medication used in the treatment of symptoms of PD, on the performance of visual tasks that depend on the ventral visual pathway. To that end, the preceding review has been intended to firmly establish that such deficits in visual tasks exist in individuals with PD, and that there are scientifically established avenues by which DA might be expected to modulate performance on these tasks, either by improving or impairing it.

Testing the prediction that administration of levodopa will alter ventral pathway-dependent function requires identifying tasks whose performance provides a meaningful indicator of that function. Face recognition, object recognition, and mental rotation of objects are all processes that are characteristic of ventral pathway function, and all three are known to be impaired in individuals with PD. Thus, a pilot test was devised using novel objects and faces as stimuli. Participants were tested on their ability to study these stimuli, remember them over a brief delay, and discriminate between studied and unstudied stimuli (of the same category), either at the learned angle or a novel angle. Task performance was then compared between a group of individuals with PD and healthy individuals of similar age.

If individuals in the PD group performed significantly worse on this task than those in the control group, then this would support the idea that ventral visual processing is impaired in individuals with PD, and that at least one processing step in this task was sufficient to demonstrate that impairment.

2.2 Methods

2.2.1 Participants

Participants recruited for this study consisted of 5 healthy older adults (ages 67 to 85 yrs.), and 7 older adults (ages 69 to 84 yrs.) who had received a clinical diagnosis of Parkinson's disease. To be eligible for participation in this study, individuals with PD were required to be between the ages of 40-85

yrs., to have been taking the same PD medication for at least the past 30 days, to score at least 24 on the Mini Mental Status Exam, and to score no greater than 18 on the Beck Depression Inventory. One participant had to be removed from the final analysis because the individual could not state with certainty that they had been on the same medication for a full 30 days (and because this individual fell asleep repeatedly during the object recognition task). Thus, data from only 6 of the 7 participants recruited for the PD group were analyzed.

2.2.2 Object Recognition Task

The object recognition task consisted of 64 trials presented on a computer monitor. Each trial consisted of a Study period and a Test period. During the Study period (2500 ms), participants were asked to study and remember an object presented on the screen. The study period was followed by a brief delay (3000 ms), and then a Test period in which participants were asked to indicate whether an object that subsequently appeared on the screen was the same as or different than the object presented in the Study period. There was no time limit on the Test period, so the second object remained on the screen until participants responded. Responses were made through a standard keyboard, with participants instructed to press “z” if they believed the object was the same, and “m” if they believed the objects were different.

The stimuli used in each trial were either monochromatic 3-dimensional renderings of faces or abstract 3-dimensional figures composed of seven cylinders of varying lengths connected end-to-end. The latter were referred to as “tube sculptures” in the instructions issued to participants. Thus, there were two different object conditions: a Face condition (32 trials) and a Tube condition (32 trials).
In addition to the two object conditions, there were also two study conditions and two test conditions. The two study conditions were Stationary, in which each stimulus remained at the 0-degree orientation for the duration of the 2500 ms Study period, and Variable, in which each stimulus was cycled through a series of three different orientations (0 degrees, 40 degrees, 0 degrees, -40 degrees, and back to 0

degrees) presented for 500 ms each. The two test conditions were Original, in which the stimulus presented in the Test period was presented in the 0-degree position (i.e., an orientation presented in the Study period), and Novel, in which the stimulus presented in the Test period was presented at either +/- 20-degrees of rotation about the z-axis (i.e., an orientation not presented in the Study period).

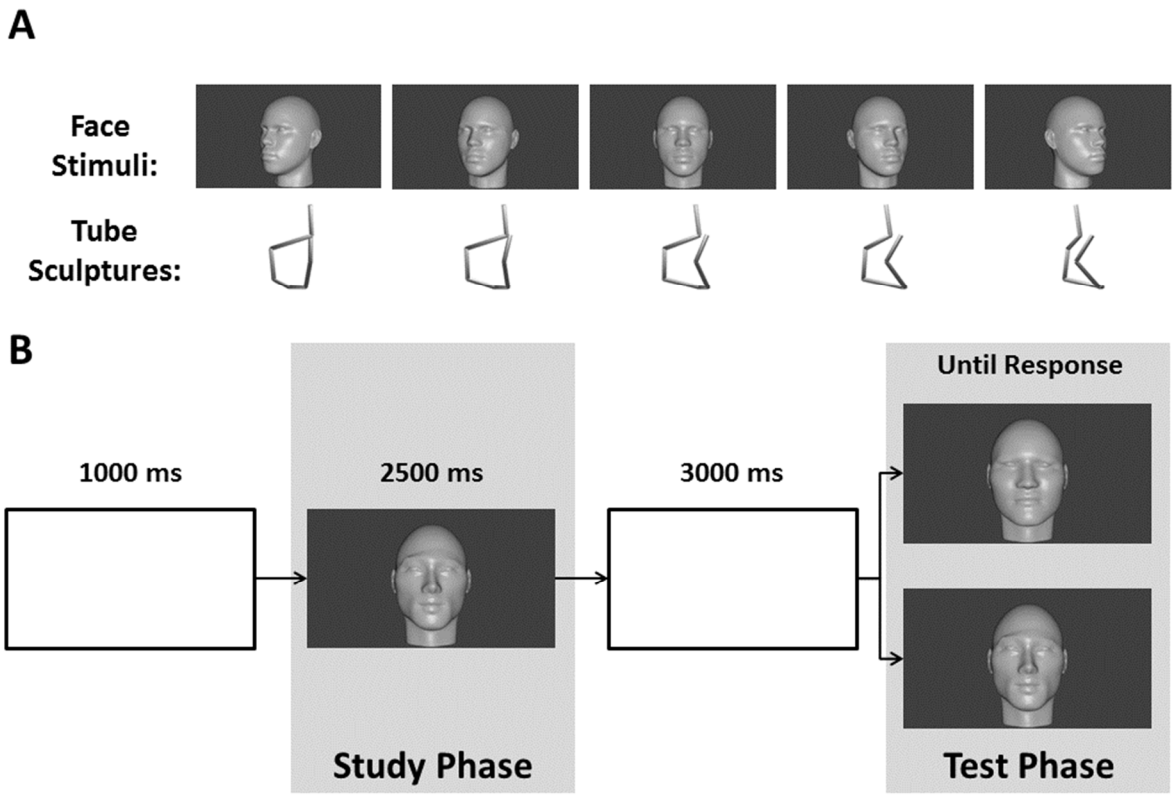


Figure 3. A: Example stimuli used in the pilot study. Figures are shown rotated at -40, -20, 0, 20, and 40 degrees about the vertical axis. B: Trial sequence for the pilot study.

2.2.2.1 Faces

Examples of the Face stimuli used in this experiment can be seen in Figure 3. To create each stimulus image, a series of photographs of human faces was first collected from Google images. All photographs were required to have closed mouths and neutral expressions. Some of the photographs used were of famous individuals, but the subsequent rendering process obscured their identities so that they were unrecognizable by the time they were presented as stimuli. Half of these photos were of men and half were of women. For each gender category, photographs were further selected on the basis of

race so that 25% of the photos were of Asian individuals, 25% were of Black individuals, 25% of the photos were of Caucasian individuals, and 25% were of Latino/Latina individuals. While the rendering process likely obscured any features that would have facilitated visual categorization into demographic groups, effort was made to ensure that the initial images represented a broad (though incomplete) cross section of individuals.

Once these photos were collected, a computer program called FaceGen (https://facegen.com/) was used to render each face onto a 3-dimensional head. This process removed all of the color and hair from the faces so that each could be distinguished only through inspection of its structural features. The process also allowed all heads to be rendered at a constant height, so that they could not be distinguished on the basis of how closely their edges came to the border of the screen.

Once these 3-dimensional heads were rendered, they were exported as .obj files and opened in Blender (http://www.blender.org), a freeware 3D art program that allowed for precise manipulation of the heads in 3-dimensional space. This allowed for the creation of images of each head rotated about the vertical axis 0-degrees (i.e., directly facing the observer), +/- 20-degrees, and +/- 40-degrees, for a total of 5 images produced from each initial photograph.

2.2.2.2 Tube sculptures

Examples of the Tube Sculpture stimuli used in this experiment can also be seen in Figure 3. These objects were based on those used by Logothetis, Pauls, and Poggio (1995). Each was created as a series of eight points that would fall within the surface of a cylinder measuring 20 units high and 10 units in diameter (i.e., all were equidistant from a central, vertical axis). These eight points were connected in serial order to form a figure composed of seven line segments. The set of points was constrained so that line segments formed by connecting them would be constrained to between 4 and 10 units, and angles formed by adjacent segments were constrained to between 90- and 120-degrees. Once each set of points was calculated and drawn using a Python script, they were rejected if the resulting figures

contained line segments that intersected, or if the figures were not sufficiently tall (i.e., at least 16 units on the z-axis). Once each set of points had been finalized, they were rendered in MatLab2016b (https://www.mathworks.com/products/matlab.html). Use of MatLab allowed not only for more complex 3-dimensional rendering of the Tube Sculptures, but also allowed for precise rotation of each object about the vertical axis. As with Face objects, images were made of each Tube Objects from five angles spaced 20-degrees apart.

2.2.3 Procedure

Upon arriving for the data collection, the researcher provided participants with a brief description of the study, after which written informed consent was obtained. All participants completed the Mini Mental Status Exam, at which point participants in the healthy control group proceeded directly to the object recognition task. Participants in the PD group also completed the Beck Depression Inventory and the Unified Parkinson's Disease Rating Scale (UPDRS) prior to completing the object recognition task. The UPDRS is an assessment of the extent to which PD symptoms interfere with an individual's projects of daily living, and is used as a measure of disease progression. The UPDRS took approximately 30 minutes to complete, after which individuals in the PD group proceeded to complete the object recognition task. The time needed to complete the object recognition task ranged from 15-20 minutes. Following the completion of all tasks, participants were debriefed.

2.3 Results

Scores between the two groups were analyzed using a simple between-subjects T-test. Overall, the PD group scored significantly lower on the task (M = 66.41%, S.E = 4.52%) than the HOA group (M = 84.69%, S.E. = 2.59%), $t(9)= 3.312$, $p=.009$. Given the relatively small sample size, and the somewhat preliminary nature of the pilot study, within-subjects T-tests were also used to assess the effectiveness of the within-subjects manipulations. Within the PD group, no significant difference in performance was observed between object type conditions (tube sculptures vs. faces, $p = .34$). Adding multiple training

views also did not seem to make a difference (p = .53), nor was there an observed disadvantage for offsetting the probe stimulus by 20 degrees (p = .73). Given that there might also have been some effects of congruency in the 3D manipulation conditions (e.g., participants might have been expected to perform better on trials with an offset probe when they had been trained on multiple views of the object), a 2 (training condition: single view vs. multiview) x 2 (probe condition: no rotation vs. 20-degree rotation) ANOVA was performed to analyze these contingencies in the PD group. However, in comparing scores across conditions no reliable interaction was observed (p = .574).

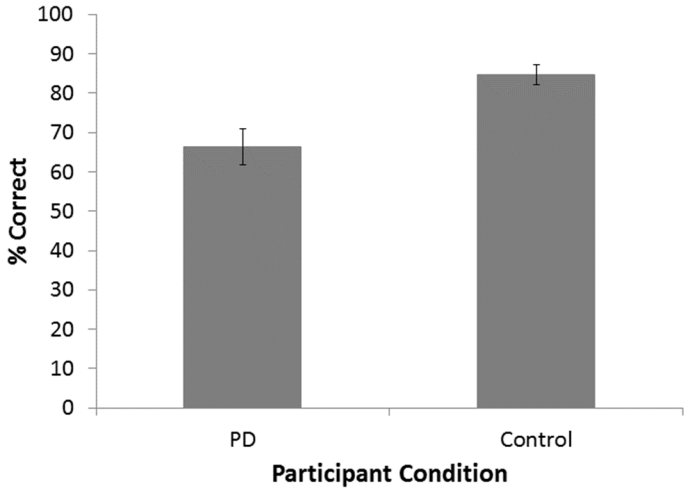


Figure 4. Between-subjects effects from the pilot study

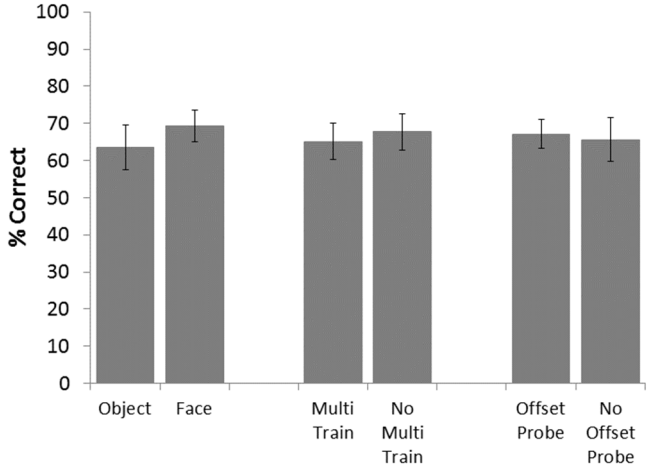


Figure 5. Within-subjects effects from the pilot study

2.4 Discussion

The results of the pilot study are consistent with the hypothesis that individuals with PD are more likely to have difficulty with face and object discrimination than their healthy counterparts. Even with a relatively small sample, some combination of the manipulations in this task was capable of modulating performance in processing of novel object and face stimuli. The efficacy of the 3D manipulations in this task was considerably less impressive. This may have had something to do with the angles at which objects were rotated. For this task, objects were presented at a maximum rotation about the vertical axis of 40 degrees. This angle was chosen as an upper limit because it was the largest rotation that was observed not to disrupt the structural descriptions of the faces or occlude their features. However, studies that have found effects of 3D rotation in individuals with PD have tended to use a much larger degree of angular rotation (e.g., Lee et al., 1998). It may therefore be advisable in future studies of mental rotation in individuals with PD to utilize a paradigm that more closely resembles one that has been shown to produce a significant effect.

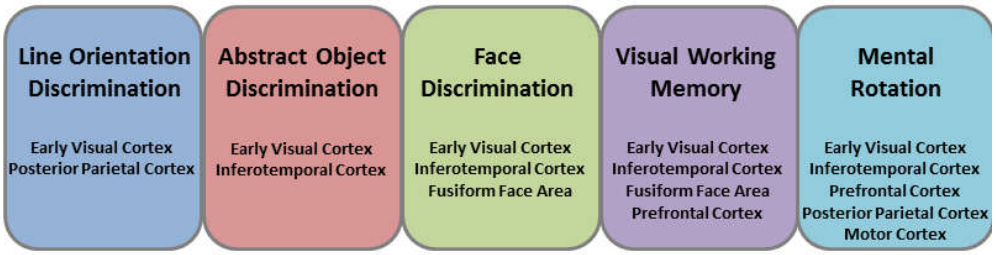
Additionally, it should be noted that several individuals in the PD condition mentioned experiencing fatigue during the object recognition task. While it is unclear whether this issue contributed to any performance deficits on this task, it might be prudent in the future to consider splitting up any visual task into blocks that can be separated by short breaks.

Because the visual task used in the pilot study was capable of capturing performance differences between individuals with PD and their matched counterparts, the researcher proceeded to the main study using a series of visual tasks based on processing steps involved in the pilot task. The goal was to determine which steps had resulted in performance deficits observed in the PD group. By testing these steps individually and measuring the effects of DA on performance, the researcher sought to determine what neural mechanisms might underlie any observed deficits, as well as any role of dopaminergic medication in mitigating or exacerbating these deficits.

CHAPTER 3: DESIGN AND JUSTIFICATION FOR CURRENT STUDY

3.1 General

This study was organized around two aims. The first aim was to determine the extent to which the performance of individuals with PD completing ventral pathway-dependent visual tasks varies between ON-meds and OFF-meds states. While individuals with PD have been shown here and elsewhere to have greater difficulty performing such tasks than their healthy counterparts, the extent to which this was a direct result of chronic DA deficiency was unknown. Also unknown was the extent to which such task performance could be modulated by the administration of levodopa. The author sought to make these determinations by examining the visual processes that comprised the pilot study individually, both following withdrawal of all antiparkinsonian medication and immediately following administration of levodopa. To contextualize the magnitude of any observed change in performance between medication conditions, performance on each task was be compared to that of a control group of healthy older adults.



Cortical Regions: **Predicted Impairments:**

Early Visual	X	X	X	X	X
Inferotemporal		X	X	X	X
Fusiform Face Area			X	X	
Posterior Parietal	X				X
Prefrontal				X	X
Motor					X

Figure 6. The pattern of task deficits predicted given different loci of brain impairment. Note that damage in each location produces a distinct combination of cognitive visual impairments.

The second aim was to use any observed medication-related performance differences on these tasks to determine the location in the brain where visual processing might be breaking down. While it is known that processing in the ventral visual pathway does not occur in a serial, hierarchical fashion, it is also known that processing resources are recruited from different visual areas as object processing becomes increasingly complex. Thus, it was hoped that differences in performance by the PD group on visual tasks of increasing complexity might be diagnostic of which abilities and ventral visual areas were affected in PD and which, if any, are relatively spared.

Given the forgoing research in which deficits on various lower visual tasks were exhibited in individuals with PD and subsequently improved under the influence of dopaminergic medication, the author hypothesized that participants in the PD group would perform better in the ON-meds condition across all five experiments. Also, since little was previously known concerning how PD might affect the visual areas recruited for these tasks, and since there was no *a priori* reason to believe that performance on any of the visual tasks would benefit disproportionately from administration of levodopa, the author hypothesized that no single brain area would be found to be responsible for performance deficits by the PD group on these five tasks.

3.2 Design Modifications from Pilot Study

The experience of running the pilot study, and subsequent feedback from colleagues, informed several changes to the procedure of the five main experiments in this study. First, multiple participants in the pilot study struggled with fatigue during the 64-trial visual task. Because the protocol for the main study used similar tasks over a much longer span of time, all five of the experimental tasks in the main study were broken up into four blocks separated by short breaks. At each break, text appeared on the computer monitor indicating the percentage of the task the participant had completed (25%, 50%, or 75%) and encouraging participants to take a moment to collect themselves and engage in physical activity or conversation before continuing if they felt it would be helpful.

Several other modifications were made to help participants adjust to the testing environment, as well as minimize stress and confusion. First, a task was added at the beginning of the Morning testing session for the sole purpose of familiarizing participants with the format of the computerized visual tasks. During this acclimation task, participants were asked to make the same sort of same/different judgments that they would be asked to make for all of the experimental tasks, but the stimuli that participants were asked to distinguish were photographs of families and landscapes that were highly discriminable. Participants used the same key mapping during the acclimation task as they would for all the experimental tasks throughout the day ("m" for same and "z" for different, or vice versa) in the hope that this would become habituated and minimize the attention required for proper responding (see section 3.4 for a full description of the procedure for the acclimation task). All participants completed the acclimation task irrespective of their experimental group. To further minimize stress and confusion in responding to the experimental tasks, the appropriate key mapping was displayed at the top of the screen every time a participant was asked to make a response. This was the case for both the acclimation task and all experimental tasks.

For the main study, the short form of the Geriatric Depression Scale replaced the Beck Depression Inventory as an indicator of depression in participants. While both scales are in common use and scores on both are strongly correlated, the Geriatric Depression Scale was designed specifically for individuals in the age range targeted for the current study, and there is evidence that the Geriatric Depression Scale is easier for older adults to complete (Olin et al., 1992). In addition, some research indicates that the Geriatric Depression Scale produces more accurate responses particularly in older women owing to its omission of questions related to sexual interest (Jefferson, Powers, & Pope, 2008).

Part of the goal for the main study was to determine what impaired perceptual process or processes was/were responsible for the relatively poor performance by individuals with PD on the pilot task. While previous research has indicated individuals with PD may display impairments on complex

visual discriminations and VWM of the type required to complete the pilot task (see section 1.5), the results of the pilot study could also be explained by individuals with PD having deficits in more fundamental visual processes, such as poor contrast sensitivity, or simply poor visual acuity. As such, Experiment 1 consisted of a line orientation discrimination task to assess the extent to which processes other than complex object discrimination might have caused the deficits observed in the pilot task. Additionally, a requirement has been added that all participants across groups must have been judged to have normal or corrected-to-normal visual acuity as determined by an eye appointment within the preceding year.

As noted previously, the rotation manipulation in the pilot study failed to produce any effect on task performance either for individuals with PD or their healthy counterparts. However, multiple other studies have documented impairments of mental rotation in individuals with PD. Examining the ability of individuals with PD to perform mental rotation, and the effect of levodopa on this process, therefore necessitated employing a different 3D manipulation. To this end, Experiment 5 is largely a replication of Lee et al. (1998), with the exceptions that a) the stimulus set used is one more recently developed by Ganis and Kievit (2015) and b) individuals with PD were tested in both ON-meds and OFF-meds states.

Finally, there is a body of research indicating that human vision is especially well-adapted for symmetry detection, so much so that this process may occur rapidly at a preattentional level (see Wagemans, 1997 for a review). Experiments 2a, 2b and 3 of the main study involve the simultaneous presentation of complex visual stimuli and ask participants to judge whether they are the same or different, and there is thus a risk that participants' performance will be driven by preattentional processing if "same" stimuli presented side-by-side create a symmetrical display, while "different" stimuli do not. It should be noted that the stimuli used in these tasks are such that there is minimal risk of identical objects producing a symmetrical visual display: the face stimuli from Experiment 2b are adapted from real photographic images and unlikely to be perfectly symmetrical themselves, and

consequently unlikely to create a perfectly symmetrical visual display when placed side-by-side on the screen. Accidental display symmetry is even less likely for the abstract objects used in Experiments 2a and Experiment 3, since the methods for creating these stimuli tend to yield objects that are themselves highly asymmetrical. However, because the stimulus sets for Experiments 2a and 2b had not been tested in other studies and the author desired to show that performance on these tasks was a result of the visual processing of objects and not a heuristic judgment of symmetry, the stimuli presented on each trial of these two tasks were slightly offset from one another in the vertical direction. This should have disrupted any accidental display symmetry that might have resulted from the simultaneous presentation of two identical objects.

3.3 Participants

Given the efficacy of levodopa in treating a variety of PD symptoms, it is not uncommon to find studies testing the effects of drug modulation that use patient samples of fewer than 10 individuals (Lee et al., 1998; Stegemöller Simuni, & MacKinnon, 2009). It is also notable that significant between-subjects effects were observed in the pilot study using a sample of only six individuals with PD and five healthy older adults. To add a margin of safety, it was decided that the study would target 15 healthy older adults and 15 older adults who have received a clinical diagnosis of PD.

To be eligible for participation in this study, all individuals were required to be between 60 and 80 years of age and to have either normal or corrected-to-normal vision as determined by an eye appointment within the last 12 months. Additionally, individuals in the PD condition were required to have received a formal clinical diagnosis of the condition. The latter were further required to be currently taking levodopa as part of their treatment regimen, and their dosage must have been stable for at least the last 30 days. Accordingly, the researcher recruited 15 individuals for the PD condition. One of these individuals mentioned during the course of the study that she was receiving deep-brain stimulation as part of her treatment regimen, and her data have not been included in the analysis,

leaving 14 in the PD condition. Subsequently, 14 healthy individuals who were age (+/- 3 years) and gender matched to individuals in the PD group were recruited. Thus, the final sample included 14 individuals with a diagnosis of PD (Age: M = 71.1, S.D. = 5.8; 5 Female, 9 Male) and 14 healthy individuals (Age: M = 70.1, S.D. = 4.9; 5 Female, 9 Male). The two groups did not differ significantly in age (p = .81) or years of education (p = .51).

Individuals in the PD group were recruited in part from a laboratory database of known volunteers and in part from reaching out to a number of support groups across the state of Iowa. Individuals in the HOA group were recruited in part from the same laboratory database and in part from general community outreach.

Table 1

Demographic Information for Participants in the Primary Study

Healthy Older Adults					Individuals with Parkinson's Disease							
ID	Sex	Age	Ed Yrs	Hand	ID	Sex	Age	Ed Yrs	Hand	UPDRS Overall	Most Affected Side	Years Since Onset
103	F	65	18	R	1	F	64	14	R	15	Right	6
109	M	75	18	R	2	M	77	12	R	67	Right	10
114	M	74	12	R	3	M	77	16	R	27	None	4
104	M	72	18	L	4	M	70	14	R	24	Right	11
101	F	69	12	R	5	F	70	12.5	R	51	None	7
119	M	63	12	R	6	M	61	24	R	63	Right	13
110	M	64	14	R	7	M	62	12	R	33	Left	6
118	F	67	12	R	8	F	70	12	R	46	None	12
102	M	67	20	R	9	M	67	16	R	39	Left	7
120	F	76	20	R	10	F	77	12	R	58	Right	8
112	M	66	16	R	12	M	67	16	R	65	Right	8
117	M	75	16	R	13	M	77	20	R	56	None	4
116	M	70	18	R	14	M	73	14	R	31	Left	16
106	F	78	16	R	15	F	75	16	R	41	Left	10
Average:		70.07	15.86		Average:		70.5	15.04				

3.4 General Procedure for Experiments

All materials and procedures were approved by the Institutional Review Board (IRB) (see Appendix A). Upon arriving for the data collection, the researcher provided participants with a brief description of the study, after which written informed consent was obtained. All participants completed the Mini Mental Status Exam and the Geriatric Depression Scale.

Participants in both the Healthy Older Adult (HOA) group and the Parkinson's disease (PD) group completed the study in two sessions during the same day: A Morning session and an Afternoon session. Depending on the preference and transportation needs of the participant, the study was conducted either at the Neurophysiology Lab at Iowa State University, at a medical facility or community center proximate to the participant's residence, or at the participant's residence. Both groups completed all five visual tasks once during each session, and lunch was provided by the experimenter in between the two sessions.

3.4.1 Procedure for PD Group

All participants in this group were provided with a copy of the Informed Consent Document prior to the day of testing, either via mail, email, or in person, and asked to read through and sign the document once they felt they adequately understood what was involved, but prior to the day of testing. It was important that informed consent be obtained prior to withdrawal from any medications to ensure that all participants were in a normal, maximally healthy state of mind. On the morning of the data collection, participants in the PD group were asked to abstain from their morning dose of all antiparkinsonian medications. However, they were instructed to take any other medications they had been currently prescribed as normal. Upon arriving at the testing location, all members of this group were conveyed to the testing room via a wheelchair to mitigate the possibility of falls or injuries. Once in the testing room, the experimenter reviewed and verified the signed Informed Consent Document and personally verified that all participants met the *a priori* exclusion criteria. Participants were then asked to complete the Mini Mental Status Exam and Geriatric Depression Scale forms, confirming that they also met these exclusion criteria. All participants in the PD group then completed the motor portion of the UPDRS to serve as an index of their PD symptoms in an OFF-meds condition. This and all portions of the UPDRS in this study were administered by the author, who was trained and certified in the procedure by the Movement Disorder Society.

Immediately following this task, participants completed a computerized task designed to help them acclimate to their surroundings and familiarize them with the format of the experimental tasks. Each of the 20 trials in the acclimation task consisted simply of the simultaneous presentation of two photographic images on a computer screen, which were either family photographs or landscapes with no people present. Participants were asked to indicate whether the two images were the same or different by pressing one of two keys on a standard keyboard. Images in the Same condition were always identical, and images in the Different condition always consisted of one family photo and one landscape to maximize ease of judgement. Participants were given as long as they needed to make a decision on each trial, and the keys that corresponded to "same" and "different" on the keyboard (either z or m) remained constant for all tasks for the remainder of the study.

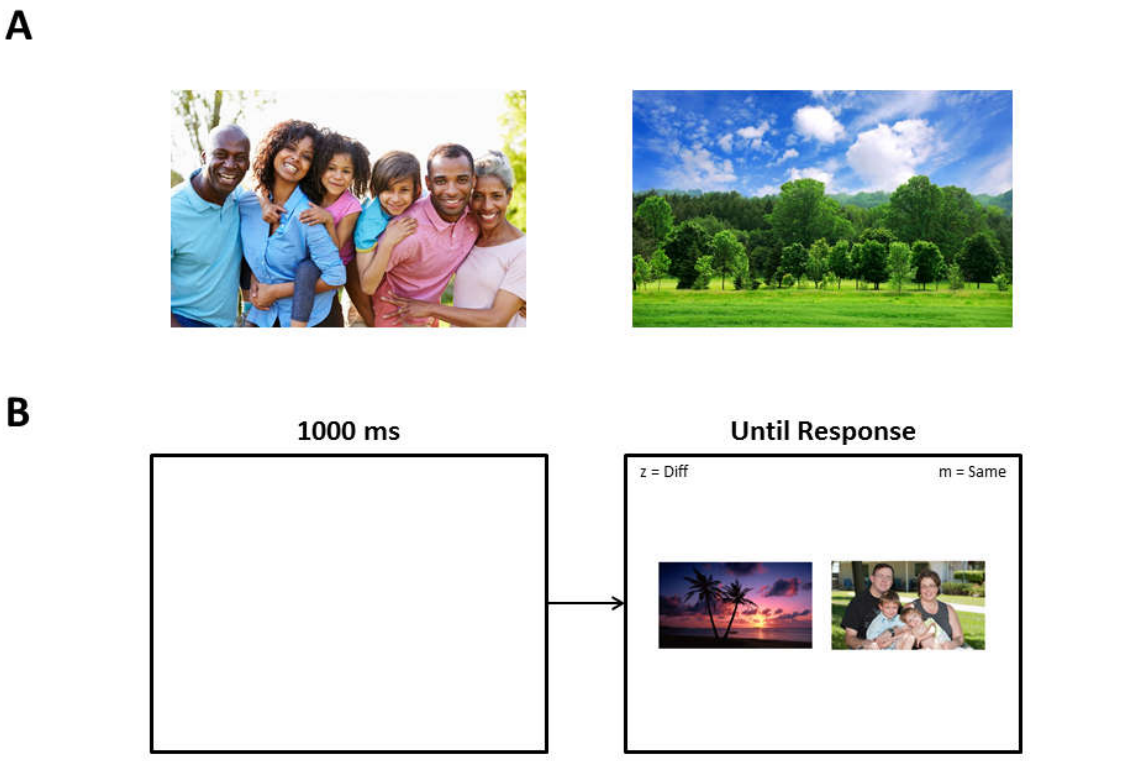


Figure 7. A: sample stimuli and B: trial sequence for Acclimation Task. Images in the Same condition were always identical, and images in the Different condition always consisted of one family photo and one landscape.

Once they had completed the acclimation task, participants in the PD group proceeded to complete all five of the computerized visual tasks. Due to the number of trials in Experiment 1, this task was divided into three parts with each administered separately. The three parts of the Experiment 1 task and the other four experiment tasks were all pooled and administered in random order.

Following completion of the first round of experimental tasks, the Morning session ended participants in the PD group were asked to take 1.5 times their standard dose of levodopa while continuing to abstain from any other antiparkinsonian medications. This procedure is common in the literature as a means bringing individuals with PD back up to standard therapeutic levels of their medication after abstention, and was endorsed by Dr. Michael S. Okun, the Chair of Neurology at the University of Florida and Medical Director of the Parkinson's Foundation, following consultation. Participants were also given the opportunity to take any additional non-antiparkinsonian medications they required during this time. Following the administration of medication, the experimenter provided participants with lunch from their choice of local venues.

Following lunch, and at least one hour following administration of levodopa, participants began the Afternoon session of the study. To this end, participants again completed all of the visual tasks from the morning session, save for the Acclimation task. All tasks were again administered in random order. Once all tasks had been completed, participants completed the full version of the UPDRS. The overall score was used as an index of their overall disease progression, while the score on the motor portion was compared to their score from the morning as an index of the effect of their levodopa medication. Once participants had completed the UPDRS, the Afternoon session was complete and participants were debriefed.

3.4.2 Procedure for the HOA Group

The procedure for individuals in the HOA group was identical to the PD group with the following exceptions:

1. Participants were not required to sign the Informed Consent Document prior to arrival at the testing location, since no withdrawal from medication was required.
2. Participants were not required to be conveyed from the parking lot to the testing room in a wheelchair.
3. Participants did not complete any portion of the UPDRS during either testing session.
4. There was no formal requirement that any participant take any medication during the course of the study, though they were allowed to take any medication they customarily took (none did).

CHAPTER 4: RESULTS OF LEVODOPA ADMINISTRATION:

Participants in the PD group for this study were asked to abstain from their morning dose of antiparkinsonian medications on the day of the study, and were asked to take 1.5 times their optimal dose of levodopa during the break between sessions to return to therapeutic levels of the drug. The motor portion of the UPDRS was administered at the beginning of the Morning session and at the end of the Afternoon session and was used as an index of how the resulting change in DA levels affected participants' PD symptoms. This subscale consists of 33 items on which participants may receive a score between 0 (does not display symptom) and 4 (most severe), for a possible (but highly improbable) score of 132. Thus, a higher score indicates worse symptoms.

The results of this experimental manipulation are shown in Fig. 7. A within subjects t-test showed a significant effect of levodopa administration, $t = -3.08$, $p < .01$, with symptoms being more severe in the morning (M = 26.86, SD = 13.83) than in the afternoon (M = 22.12, SD = 11.38). However, as Fig. 7 shows, there was appreciable variation between individuals, with two participants showing modestly worse symptoms during the Afternoon session.

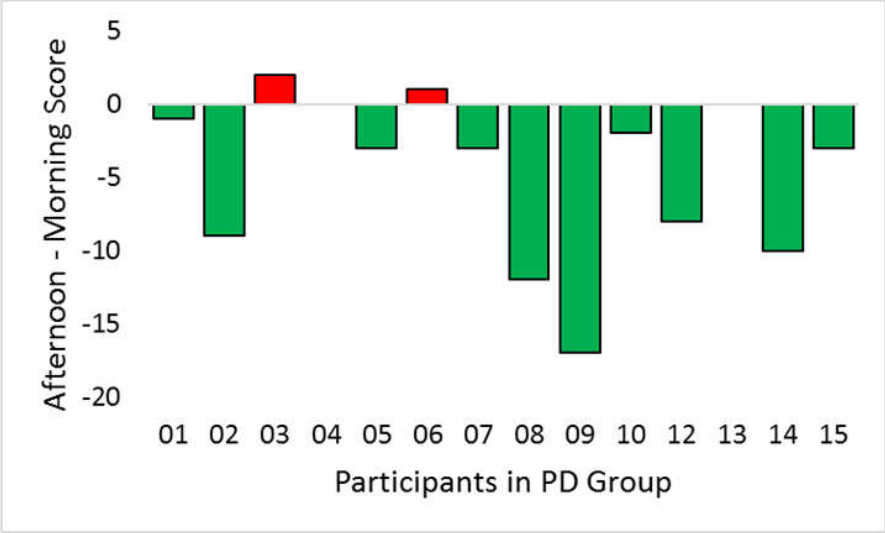


Figure 8: The effects of levodopa administration on participants' Motor scores on the UPDRS. Scores on this scale increase with symptom severity, so a negative score on this graph represents an improvement in symptoms.

CHAPTER 5: EXPERIMENT 1

5.1 Background

While the human visual system is known to rely on recursive rather than strictly serial processing, it is still acknowledged that there are higher levels of visual processing that require successful processing at lower levels to perform their function (Gilbert & Li, 2013; Vidyasagar & Eysel, 2015). The progressive nature of visual processing can thus complicate visual studies because individuals may perform equally poorly on a complex task (e.g., face discrimination) in cases where they have deficits in lower visual processing (e.g., macular degeneration) and cases where they have deficits in higher processing (e.g., prosopagnosia).

As noted above, multiple studies have found that individuals with PD tend to perform worse on line discrimination tasks than their healthy counterparts (Montse et al., 2001; Uc et al., 2003). Additionally, the comparatively poorer performance on the pilot task by individuals in the PD group could be equally well explained by damage to one or more of the myriad lower visual processing steps on which this task is likely to depend. It also has not escaped notice that broad array of visual deficits observed in individuals with PD make the idea of a more fundamental common cause intuitively appealing. Therefore, in addition to the requirement that all participants in this study possess normal or corrected-to-normal vision, this study included a line orientation discrimination task to assess participants' ability to differentiate between more basic visual features. While the ability of individuals with PD to perform this task as well as their healthy counterparts would not prove that poor performance by the former on complex visual tasks was not due to deficits in lower-order visual processing, an inability of the former to perform this task as well as healthy control participants would need to be considered when interpreting the results of more complex tasks. For instance, if individuals with PD performed significantly worse than healthy individuals on the mental rotation task, but a similar group effect was found on the line orientation task and the effect sizes were comparable, then it would

be problematic to conclude that the observed deficit in mental rotation was a mental rotation impairment *per se*. Rather, it could simply be the downstream effect of a more basic visual impairment.

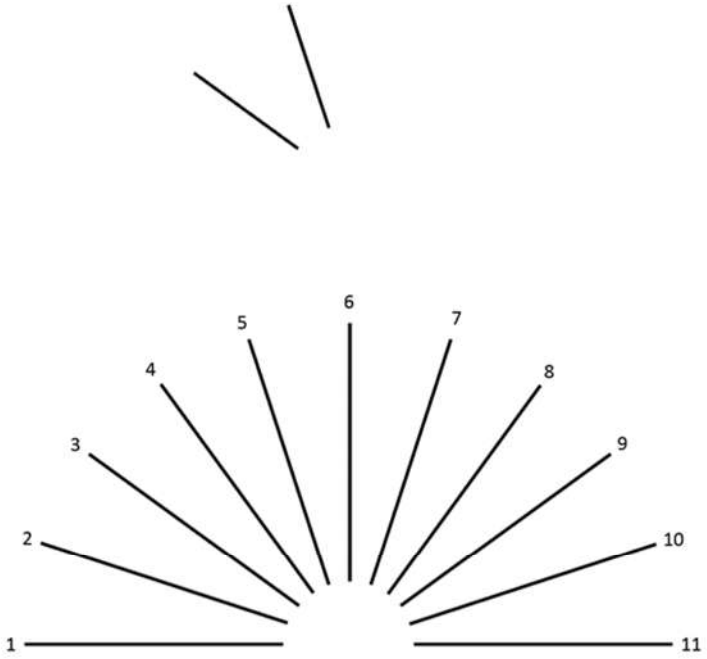


Figure 9. Example stimuli similar to the Benton Judgment of Line Orientation Test. Participants are asked to indicate which two lines on the bottom array match the orientations of the above lines.

The most commonly referenced line discrimination task in the current literature is the Benton Judgment of Line Orientation (JLO) Test (Ska, Poissant, & Joanette, 1990; Montse et al., 2001; Tranel et al., 2009) (see Fig. 9). In this task, participants view an array of 11 reference lines with adjacent lines rotated by 18 degrees (Benton, Varney, & Hamsher, 1978). They are then shown two target lines of shorter length on a different page and asked to indicate the two reference lines rotated at the same angles as the target lines. Participants are given an unlimited amount of time to make this judgment. While this task has been used in a variety of studies examining the effects of PD (e.g., Levin et al., 1991; Finton, Lucas, Graff-Radford, & Uitti, 1998; Montse et al., 2001), the judgment participants were asked to make in the JLO differed sufficiently from that of the pilot study for the present research that the creating of a new task was desirable. Specifically, the JLO is a matching task requiring participants to

select a similarly oriented line from an array of alternatives, whereas the present study is aimed at investigating discriminability. The JLO also requires participants to make two correct judgments (one for each target line) for a trial to be scored as correct, which complicates the interpretation of results.

While this experiment was intended to inform the interpretation of other experiments in this study, any evidence of a line orientation discrimination deficit in individuals with PD by itself is difficult to interpret from a neuropsychological standpoint. It has long been known that there are cells located in the primary visual cortex of cats (Hubel & Wiesel, 1959) and non-human primates (Hubel & Wiesel, 1968) that respond selectively to bars of light and edges of particular sizes and orientations. However, more recent research has shown that cells earlier in the visual systems of many mammals display signs of orientation selectivity, including some LGN and retinal ganglion cells (Vidyasagar & Eysel, 2015; Nath & Schwartz, 2016). To complicate matters further, an imaging study conducted by Tranel et al. (2009) examining the performance of patients with brain lesions on the JLO revealed that the damaged areas most associated with diminished task performance were the right angular gyrus and areas of the dorsal visual stream, including the posterior region of the supramarginal nucleus. So, while it has been shown that performance on the JLO improves in individuals with PD following pallidotomy (Junqué et al., 1999), the neural underpinnings of any differences in line orientation discrimination between individuals with PD and healthy individuals, as well as between individuals with PD in an ON-meds vs. OFF-meds state, is beyond the scope of this study. The goal of this experiment was simply to determine the extent to which any observed impairment on higher visual tasks could be reasonably attributed to dysfunction in higher visual areas.

5.2 Methods

5.2.1 Participants

All participants from the study sample completed this experiment and were included in the analysis. See section 3.3 for details concerning sample characteristics and recruitment methods.

5.2.2 Stimuli

Stimuli consisted of pairs of white line segments set against a black background. The longer dimension of each line segment covered three degrees of visual angle, and the gap between pairs of segments was also three degrees. On each trial, one line segment was rotated in the picture plane between 0 and 90 degrees from horizontal by some multiple of 10 (e.g., 10 degrees, 20 degrees, 30 degrees, etc.). On half of the trials, the second line segment was at the same angle as the first (i.e., rotated at 0 degrees with respect to the first segment) while on the other half of trials the second line segment was rotated between 10 and 90 degrees with respect to the first, again by some multiple of 10 degrees.

5.2.3 Procedure

During this task, participants saw two line segments appear simultaneously on a computer monitor, and were asked to indicate whether the two segments were positioned at the same orientation. The task consisted of 180 trials, but was administered in three installments of 60 trials each to minimize any effects of fatigue or proactive interference.

Each trial began with a blank screen that persisted for one second, followed by the simultaneous presentation of two white horizontally aligned line segments. Half of all participants pressed the “z” key if they believed that the two lines were at the same angle on the screen and pressed the “m” key if they believed the two lines were at different angles, while for half of participants this mapping was reversed. There was no pre-set time limit on each trial, so the stimuli remained on the screen until the participants responded. Each of the three installments of this task was divided into blocks of 15 trials, between which the experiment paused and encourage participants to take a break for as long as they liked prior to resuming.

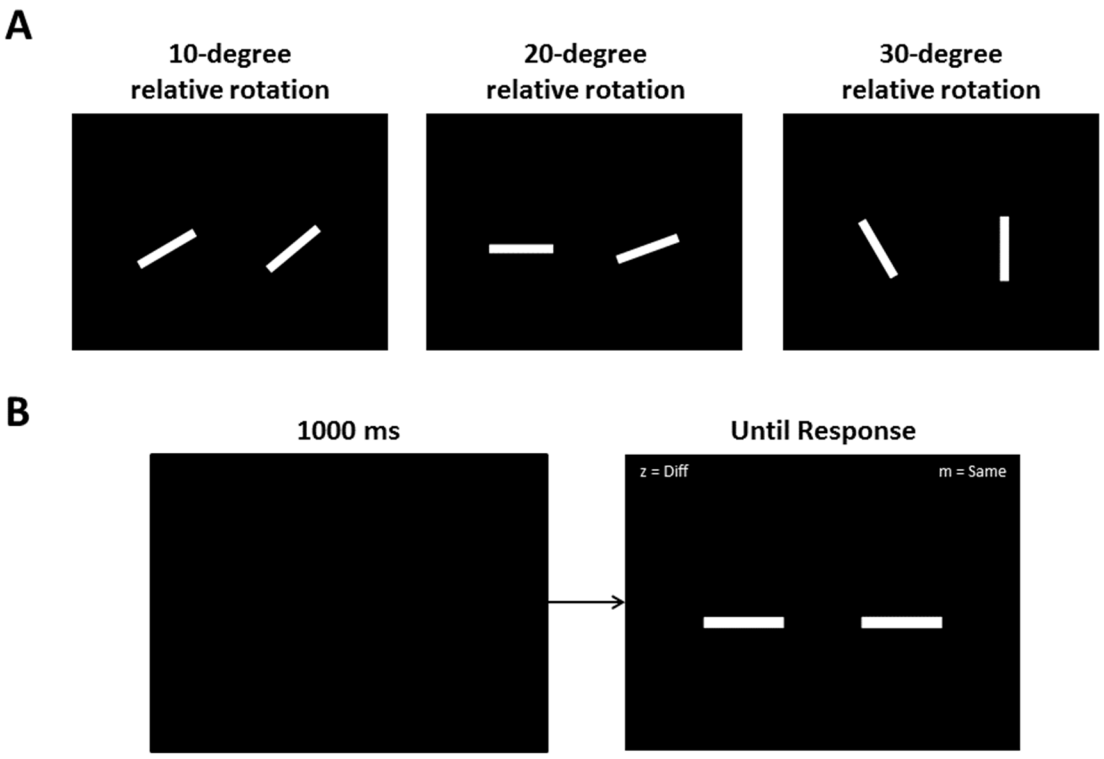


Figure 10. A: Sample stimuli and B: trial sequence for Experiment 1. The angle between the two line segments varied between 0 and 90 degrees by increments of 10 degrees. Rotation is within the picture plane.

5.3 Results

The effects of PD pathology and levodopa treatment on line orientation discrimination were examined using a 2 (Group: PD vs. HOA) x 2 (Session: Morning vs. Afternoon) ANOVA. The results of this analysis are shown in Fig. 10. There was a main effect of Group, $F(1,26) = 12.74$, $p = .001$, $\eta^2_p = .329$.,

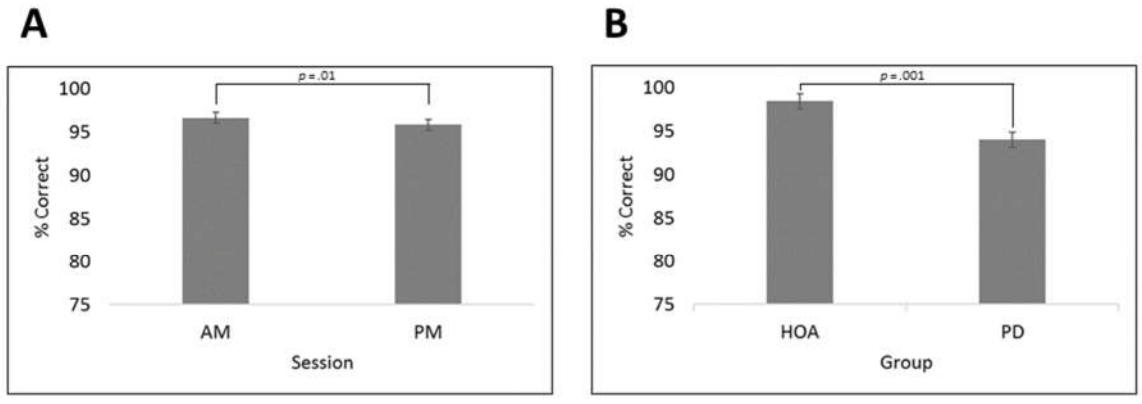


Figure 11. Overall performance on the line discrimination task. A: Main effect of Session. B: Main effect of Group. Error bars represent standard errors.

with the HOA group (M = 98.45%, S.E. = .88%) scoring higher on the task than the PD group (M = 94.01%, S.E. = .88%). There was also a main effect of Session, $F(1,26)$, $p = .01$, $\eta^2_p = .223$, with participants across groups performing modestly better in the Morning (M = 96.63%, S.E = .64%) than the Afternoon (M = 95.83%, S.E. = .64%) session. No other effects or interactions rose to the level of significance.

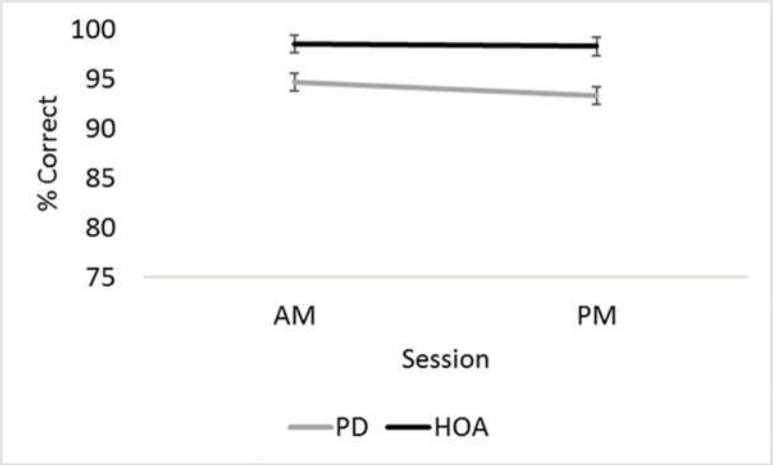


Figure 12. Non-significant two-way interaction from the overall results of Experiment 1. The interaction between Group and Session did not rise to the level of significance. Error bars represent standard errors.

To analyze the kinds of errors made by the two groups, an additional analysis was conducted to examine participants' performance at different angles of rotation. To simplify this analysis and its interpretation, trials in which the lines were positioned at 0 degrees relative rotation were omitted, and the remaining rotation angles were grouped into Small (10, 20, and 30 degrees), Medium (40, 50 and 60 degrees) and Large (70, 80, and 90 degrees), resulting in a 2 (Group: PD vs. HOA) x 2 (Session: Morning vs. Afternoon) x 3 (Angle: Small, Medium, and Large) mixed factorial ANOVA. This analysis again revealed a main effect of Group, $F(1,26) = 13.45$, $p = .001$, $\eta^2_p = .341$, with the HOA group (M = 97.78%, S.E. = .96%) making more correct judgments than the PD group (M = 92.78%, S.E. = .96%). There was also a main effect of Session, $F(1,26) = 5.24$, $p = .03$, $\eta^2_p = .168$, with participants across groups performing better in the morning (M = 95.91%, S.E. = .65%) than the afternoon (M = 94.64%, S.E. =

.81%). Additionally, this analysis revealed a main effect of Angle, $F(2,52) = 23.491$, $p < .001$, $\eta^2_p = .475$, with participants across groups performing worse on trials with Small angles of rotation (M = 89.58%, S.E. = 1.69%) than either Medium (M = 98.63%, S.E. = .37%) or Large (M = 97.62%, S.E. = .70%) rotations. The interaction between Angle and Group was also significant, $F(2,52) = 4.34$, $p = .02$, $\eta^2_p = .143$. Specifically, while both groups performed more poorly on Small than Medium trials, the PD group also performed more poorly on Small than Large trials, while no corresponding difference was observed for the HOA group.

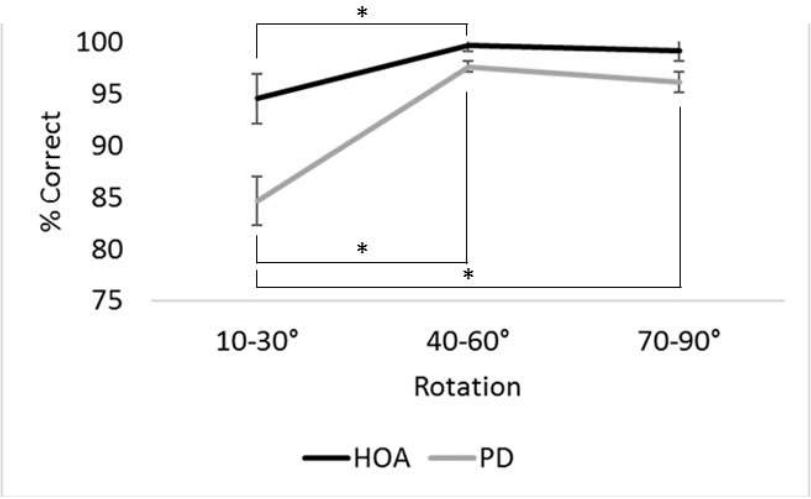


Figure 13. Interaction between Group and Angle in the line discrimination task. Error bars represent standard errors.

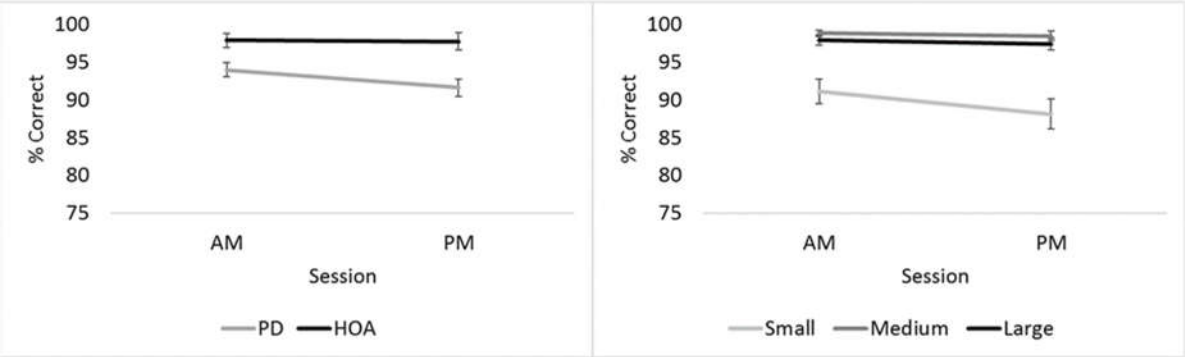


Figure 14. Non-significant two-way interactions from the analysis of error types in Experiment 1. A: Group by Session. B: Angle by Session. Error bars represent standard errors.

The relationship between levodopa administration and task performance for individuals in the PD group was also assessed by calculating difference scores for the line discrimination task and the motor portion of the UPDRS between sessions and performing a correlational analysis. The correlation did not reach significance either when all participants were analyzed (p = .94) or when participants whose UPDRS motor scores did not improve for the afternoon session were removed (p = .52). Finally, overall performance by the PD group during the Afternoon session (i.e., when they were ON-meds) was examined for any relationship with their disease progression. There was a trend toward a negative correlation between task score and UPDRS score, but this association did not reach the level of significance (p = .05), and no correlation was observed between task score and years since disease onset (p = .88).

5.4 Discussion

The goal of this experiment was to examine the possibility that the results observed in the pilot study, and by extension other complex visual tasks, could be explained by more basic visual deficits in individuals with PD. The results of Experiment 1 indicate that some of the of the observed differences between individuals with PD and their healthy counterparts may be accounted for by deficits in basic feature discrimination. The difference in performance between the PD and HOA groups was significant for this task, and a probable ceiling effect for both groups may have masked the full extent of this difference. This result is consistent with the findings of several studies indicating that individuals with PD performed worse than their healthy counterparts on the Benton JLO task (Montse et al., 2001; Finton et al., 1998).

Aim 1 of the current study was to examine any effect of DA and dopaminergic medications on visual processing. Given the design of Experiment 1, such an effect would most likely appear as an interaction between group and session, where the administration of levodopa medication between sessions would affect individuals with PD in a way not similarly observed in the HOA group. The

researcher predicted that scores for the PD group would increase in the Afternoon session compared to the Morning session, while the HOA group would show either no increase or a proportionally smaller increase. Instead, both groups did slightly worse in the Afternoon session than the Morning, so there was no discernible effect of levodopa administration for this task. The only other experimental task in this study to show any effect of Session was Experiment 2a, in which the PD group, but not the HOA group, showed slightly diminished performance in the afternoon. Interestingly, these were the two tasks for which a ceiling effect was observed, indicating that the observed performance decrements may have been the result of boredom or fatigue.

The pattern of results for this experiment raises the possibility that lower performance by the PD group on this task may not be the result of deficient feature discrimination as such, but instead of some yet more fundamental visual process that is adversely affected in PD. However, several factors make this unlikely. First, the requirement that all participants in this study, irrespective of group, possess either normal or corrected-to-normal vision should minimize the possibility that differences in performance were the result of diminished visual acuity in those in the PD group. Further, the use of white stimuli against a black background resulted in the maximum possible contrast, meaning that group differences cannot be explained by poorer contrast sensitivity in the PD group. Attentional deficits are also unlikely to account for the difference, since both groups were given unlimited time to study the stimuli and respond. Finally, while there is always a possibility when studying a sample of individuals with motor difficulties that mis-keying or other difficulties in responding could account for group differences, the non-random nature of the errors in this case makes this unlikely. The interaction observed between group and angle in the second analysis indicates that the group difference arises disproportionately from trials with smaller angles of rotation where more difficult discriminations were required, whereas motor difficulties would likely be more equally distributed across trial types. The

researcher therefore posits that differences in performance between the PD and HOA group for this task were due to impaired stimulus discrimination per se, and not some other extraneous variable.

It is notable that the group difference in Experiment 1 is appreciably smaller than that observed in the pilot study, indicating that impairments in basic feature discrimination cannot account entirely for the difference observed between groups on the pilot task. However, feature discrimination deficits of some in the PD group likely account for some portion of this group difference, and thus will have to be taken into account when interpreting Experiments 2 through 4.

Aim 2 of the present study was to examine the neural basis of visual impairments observed in individuals with PD. As stated at the outset of this experiment, the precise neural correlates of performance on this task are difficult to pin down, with a variety of areas implicated across multiple studies (Nath & Schwartz, 2016; Vidyasagar & Eysel, 2015; Tranel et al., 2009; Hubel & Wiesel, 1959). Previous research indicates that the areas of the healthy brain most likely to be necessary for line discrimination are the primary visual cortex (Hubel & Wiesel, 1959) and areas in the right parietal cortex (Tranel et al., 2009), and several studies have suggested that individuals with PD may have marked grey matter loss in these areas (Melzer et al., 2011; Pereira et al. 2009). Pereira and colleagues go so far as to suggest that many of the visuospatial and visuoperceptual difficulties observed in individuals with PD are driven by grey matter losses (Pereira et al., 2009). However, the participants in the PD group for both Periera et al. (2009) and Melzer et al. (2011) had more severe pathology than those analyzed in the present study, and other studies have implicated BG-specific pathology in impairments of line orientation judgment (Junqué et al., 1999). We therefore turn to Experiments 2 through 4 to gain a better picture of the neural mechanisms involved in impaired perception of visual objects.

CHAPTER 6: EXPERIMENTS 2a AND 2b

6.1 Background

The presence of DA receptors throughout the cortex (Hurd, Suzuki, & Sedvall, 2001), the reciprocal connectivity between the BG and IT (Middleton & Strick, 1996), and the pattern of visual deficits observed in previous studies (Weil et al., 2016) raise the possibility that PD may lead to impaired processing in IT. Visual processing in IT (and area TE in particular) is generally considered to involve the most complex purely visual representations of stimuli in the ventral stream of primates (Tanaka et al., 1991; Tsunoda et al., 2001; Lehky & Tanaka, 2016). Neurons in this area have been found to selectively respond to complex visual features or feature sets of objects. For instance, Logothetis, Pauls, and Poggio (1995) measured from 970 IT cells while macaques were presented with a series of complex objects that included wire and amoeboid objects. These researchers found that of the 796 neurons that were activated by stimulus presentation, some (n = 169) fired preferentially to wire objects while others (n = 58) responded preferentially to amoeboid objects. Further, subsets of neurons were found that responded selectively to a subset of views of a specific object (those nearest to a learned perspective; n = 93) and others responded selectively to specific stimuli irrespective of the viewer's perspective (n = 3). In another study, Tsunoda et al. (2001) made electrophysiological recordings of dorsal TE in macaque monkeys, including extracellular recordings of individual neurons and intrinsic signal imaging to measure activation over a wider cortical region. The latter method revealed "spots" approximately 0.5 x .035 nm that selectively responded to objects with common features, such as ellipses or rectangles. These and other studies have led researchers to conclude that complex features of objects are represented in columns of neurons in IT, and whole objects are represented using a population code that binds these columns together (Tsunoda et al., 2001; Lehky & Tanaka, 2016).

The foregoing account is consistent with several lesion studies that have examined patients with damage to occipitotemporal areas that has largely spared the primary visual cortex. Though lesions that

occur outside of a controlled laboratory setting are rarely confined to IT, lesions that include IT have been observed to lead to a condition known as apperceptive agnosia, in which individuals show impaired recognition for objects but relatively intact basic visual functioning (Warrington & James, 1988; Grossman, Galetta, & D'Esposito, 1997) For instance, a study by Grossman, Galetta, and D'Esposito (1997) examined two patients with bilateral damage to middle and inferior temporooccipital cortices. Both individuals showed significant impairments in object recognition, such as naming common objects depicted in line drawings, and match-to-sample tasks that used stimuli such as faces and partially overlapping geometric shapes. In both cases, the ability to match simple geometric shapes, as well as the ability to draw letters, words, and simple geometric stimuli from memory was relatively (but not completely) preserved.

There is a body of research indicating that some classes of stimuli are processed differently from one another in IT. The most commonly cited example is the processing of faces, in which recognition can be disrupted by manipulations (e.g., inversion, presentation in photo negative, etc.) to which the recognition of other objects is robust (Farah, Levinson, & Klein, 1995; Farah, et al., 1995; Cooper & Wojan, 2000). Indeed, there is an area of the fusiform gyrus in IT known as the fusiform face area, which has been posited to be dedicated to the processing of human faces (Kanwisher, McDermott, & Chun, 1997; McCarthy et al., 1997). Controversy remains about whether this sort of privileged processing is restricted to faces, or whether it also extends to other classes of objects for which the user has developed expertise (Gauthier et al., 1997), or to any class of stimuli that share a common structural description (Lehky & Tanaka, 2016), and a resolution is beyond the scope of the present study. However, in testing the effects of PD and levodopa on processing in IT, it was deemed instructive to test discriminations both of a class of stimuli discriminable by structural description, and a class of stimuli with a uniform structural description. Accordingly, Experiment 2a examines the ability of participants to discriminate between stimuli based on the wire objects in Logothetis, Pauls, and Poggio (1995) (i.e.,

figures composed of a repeated visual primitive randomly arranged), while Experiment 2b examines the ability to discriminate between 3D-rendered human faces.

6.2 Experiment 2a Methods

6.2.1 Participants

All participants from the study sample completed this experiment and were included in the analysis. See section 3.3 for details concerning sample characteristics and recruitment methods.

6.2.2 Stimuli

The stimuli used in this experiment were a new set of tube sculptures generated by the same method as those in the pilot study. Each was created as a series of eight points that would fall within the surface of a cylinder measuring 20 units high and 10 units in diameter (i.e., all were equidistant from a central, vertical axis). These eight points were connected in serial order to form a figure composed of seven line segments. The set of points was constrained so that line segments formed by connecting them would be limited to between 4 and 10 units in length, and angles formed by adjacent segments were constrained to between 90- and 120-degrees. Once each set of points was calculated and drawn using a Python script, they were rejected if the resulting figures contained line segments that intersected, or if the figures were not sufficiently tall (i.e., at least 16 units on the vertical axis). Once each set of points had been finalized, they were rendered in MatLab2016b (https://www.mathworks.com/products/matlab.html). Conversion of these 3D-rendered images into .png files suitable for ePrime 2.0 was accomplished using a free open source graphics program called Blender (https://www.blender.org/).

6.2.3 Procedure

This task was composed of 72 trials. Each trial began with a blank screen that persisted for one second, followed by the simultaneous presentation of two tube sculptures slightly offset about the horizontal axis. Half of all participants pressed the “z” key if they believed that the two sculptures were

the same and pressed the “m” key if they believed the two sculptures were different, while the other half of participants received the reverse key mapping. There was no pre-set time limit on each trial, so the stimuli remained on the screen until the participants responded. The task was delivered in four equal-sized blocks, between which the experiment paused, informed participants of their progress, and encourage them to take a break for as long as they liked prior to resuming.

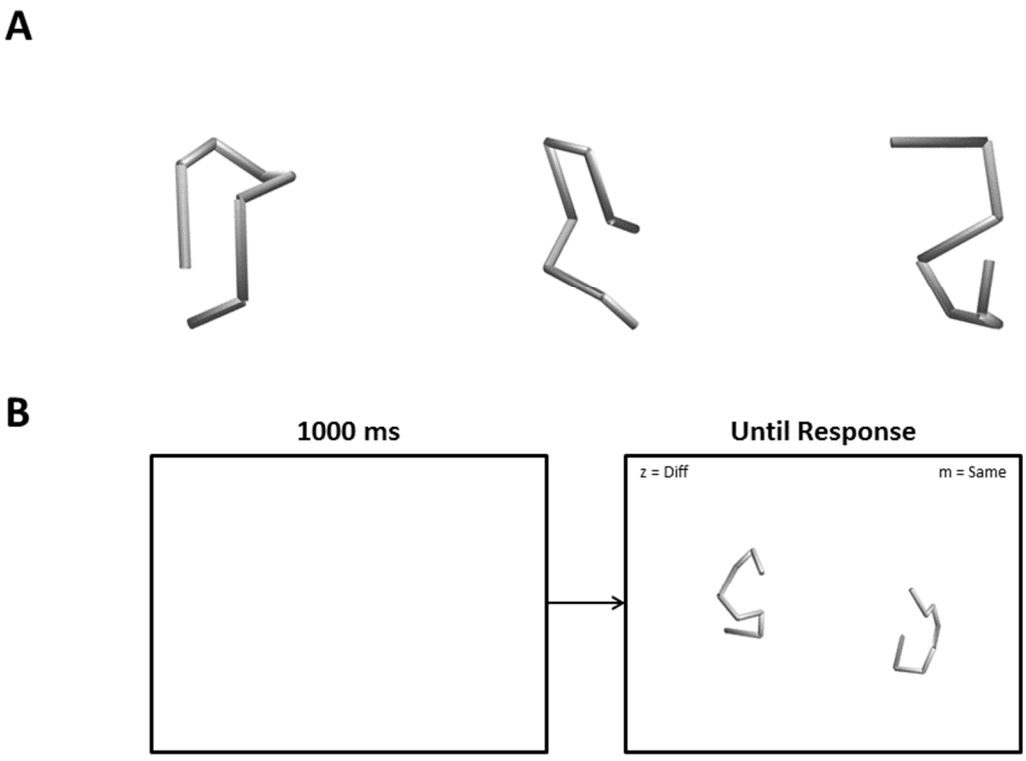


Figure 15. A: sample stimuli and B: trial sequence for Experiment 2a. The stimuli were the same as those used in the pilot study, but were shown only at 0 degrees rotation. Discrimination was made between simultaneously presented stimuli.

6.3 Results of Experiment 2a

The effects of PD pathology and levodopa treatment on object discrimination were examined using a 2 (Group: PD vs. HOA) x 2 (Session: Morning vs. Afternoon) ANOVA. There was a main effect of Group, $F(1,26) = 6.37$, $p = .02$, $\eta^2_p = .197$, with the HOA group (M = 99.45%, S.E. = .45%) scoring higher on the task than the PD group (M = 97.87%, S.E. = .45%). The interaction between Session and Group was

also significant, $F(1,26) = 5.65$, $p = .03$, $\eta^2_p = .178$, with the PD group performing better in the Morning than the Afternoon, but no corresponding difference in the HOA group.

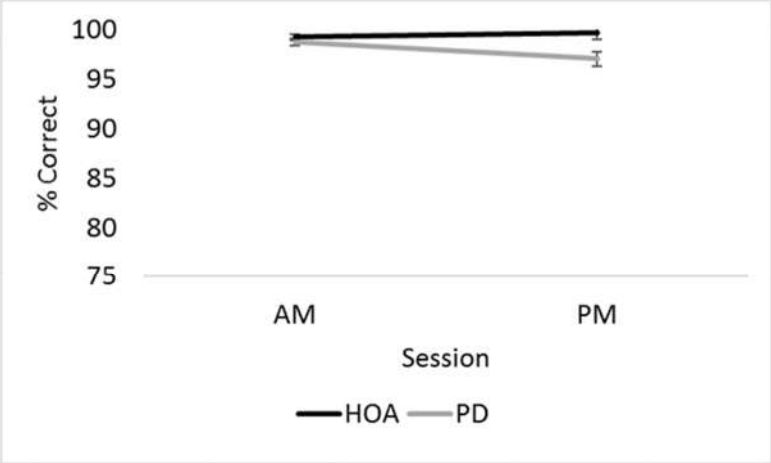


Figure 16. Interaction between Group and Session in the object discrimination task. Error bars represent standard errors.

The relationship between levodopa administration and task performance for individuals in the PD group was also assessed by calculating difference scores for the object discrimination task and the motor portion of the UPDRS between sessions and performing a correlational analysis. The correlation did not reach significance either when all participants were analyzed ($p = .86$) or when participants whose UPDRS motor scores did not improve for the afternoon session were removed ($p = .68$). Overall performance by the PD group during the Afternoon session was again examined for a relationship with PD progression. No relationship was observed between task performance and either UPDRS scores ($p = .51$) or years since disease onset ($p = .51$).

6.4 Methods for Experiment 2b

6.4.1 Participants

All participants from the study sample completed this experiment and were included in the analysis. See section 3.3 for details concerning sample characteristics and recruitment methods.

6.4.2 Stimuli

The stimuli used in this experiment were a new set of face stimuli generated by the same method as those in the pilot study. To create each stimulus image, a series of photographs of human faces was first collected from Google images. All photographs were required to have closed mouths and neutral expressions. Some of the photographs used were of famous individuals, but the subsequent rendering process obscured their identities so that they were unrecognizable by the time they were presented as stimuli (the researcher dares you to correctly identify one). Half of these photos were of men and half were of women. While the rendering process likely obscured any features that would have facilitated visual categorization into demographic groups, effort was made to ensure that the initial images represented a broad (though incomplete) cross section of individuals. Thus, for each gender category, photographs were further selected on the basis of race and region of origin so that the full stimulus set contained equal numbers of Asian, Australian Aboriginal, Black, Caucasian, Latina/o, and Middle Eastern individuals. Once these photos were collected, a computer program called FaceGen (https://facegen.com/) was used to render each face onto a 3-dimensional head. This process removed all of the color and hair from the faces so that each could be distinguished only through inspection of its structural features. The process also allowed all heads to be rendered at a constant height, so that they could not be distinguished on the basis of how closely their edges came to the border of the screen. Once these 3-dimensional heads were rendered, they were exported as .obj files and opened in Blender (http://www.blender.org), a freeware 3D art program that allowed for precise manipulation of the heads in 3-dimensional space.

6.4.3 Procedure

This task was composed of 72 trials. Each trial began with a blank screen that persisted for one second, followed by the simultaneous presentation of two horizontally aligned face stimuli. Half of all participants pressed the “z” key if they believed that the two stimuli were the same and pressed the “m”

key if they believed the stimuli were different, while the other half of participants were assigned the reverse key mapping. There was no pre-set time limit on each trial, so the stimuli remained on the screen until the participants responded. The task was delivered in four equal-sized blocks, between which the experiment paused, informed participants of their progress, and encourage them to take a break for as long as they liked prior to resuming.

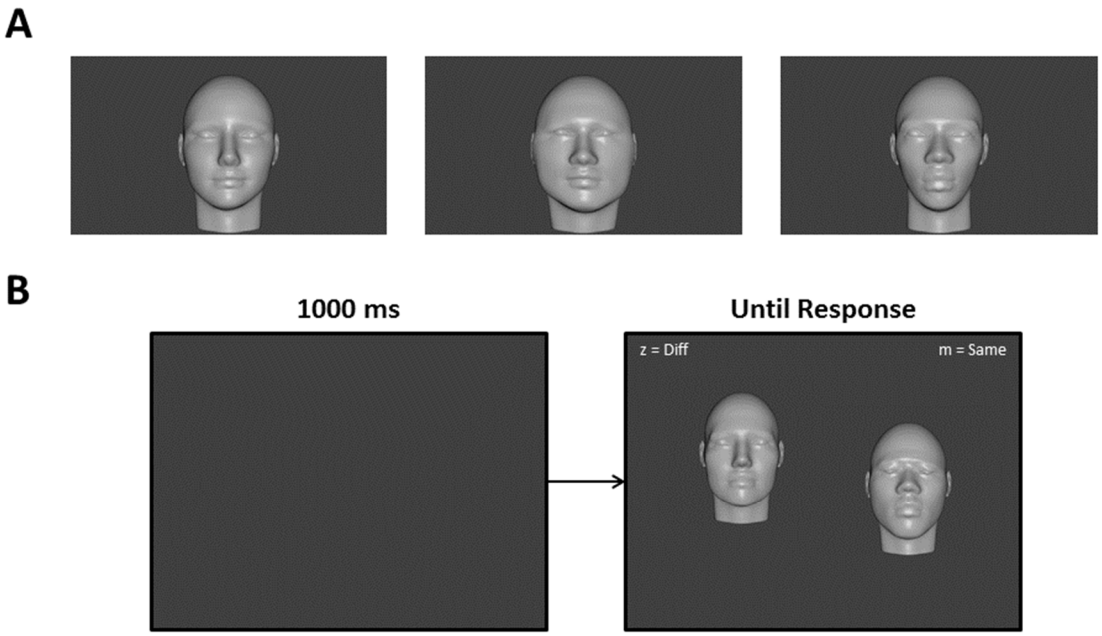


Figure 17. Trial sequence for Experiment 2b. Face stimuli were the same as those used in the pilot study, but were shown only at 0 degrees rotation, and discrimination was made between simultaneously presented stimuli.

6.5 Results of Experiment 2b

The effects of PD pathology and levodopa treatment on face discrimination were examined using a 2 (Group: PD vs. HOA) x 2 (Session: Morning vs. Afternoon) ANOVA. The results showed a main effect of Group, $F(1,26) = 10.71$, $p < .01$, $\eta^2_p = .292$, with the HOA group (M = 95.39%, S.E. = 1.51%) scoring higher on the task than the PD group (M = 88.39%, S.E. = 1.51%). No other effects or interactions were significant.

The relationship between levodopa administration and task performance for individuals in the PD group was also assessed by calculating difference scores for the face discrimination task and the

motor portion of the UPDRS between sessions and performing a correlational analysis. The correlation did not reach significance either when all participants were analyzed (p = .86) or when participants whose UPDRS motor scores did not improve for the afternoon session were removed (p = .65). Overall performance by the PD group during the Afternoon session was again examined for a relationship with PD progression. No relationship was observed between task performance and either UPDRS scores (p = .51) or years since disease onset (p = .94).

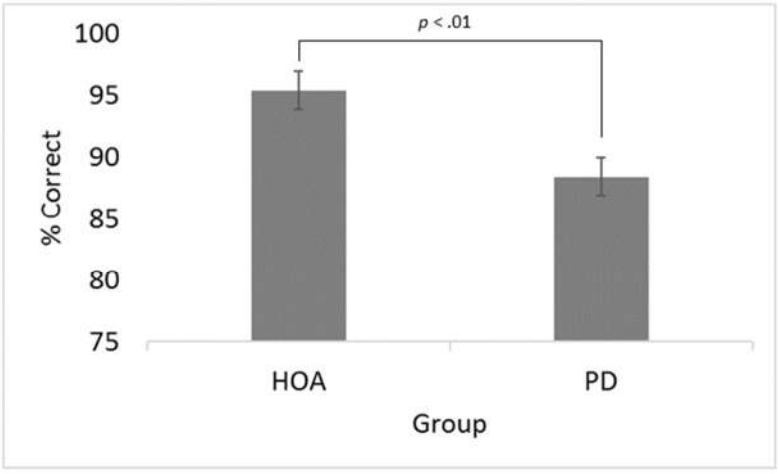


Figure 18. Main effect of Group for the face discrimination task. Error bars represent standard errors.

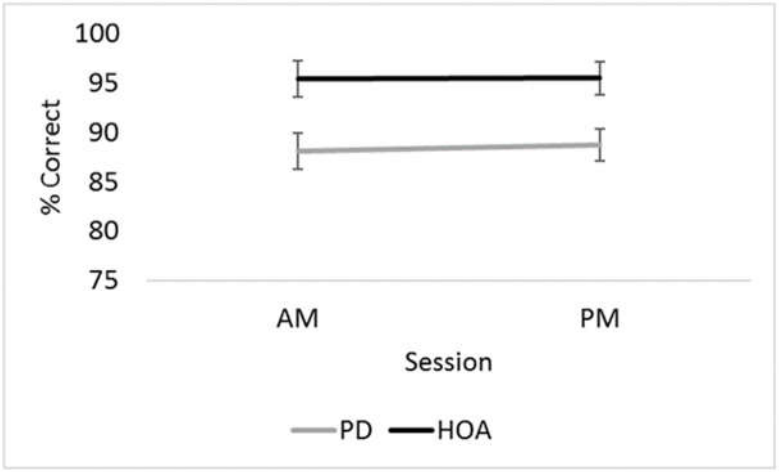


Figure 19. Non-significant two-way interaction from Experiment 2b. The interaction between Group and Session did not rise to the level of significance. Error bars represent standard errors.

6.6 Discussion of Experiments 2a and 2b

The results of both Experiment 2 tasks support the hypothesis that individuals with PD are impaired at making discriminations of complex visual objects compared to their healthy counterparts. While an initial examination of the mean differences between groups for both tasks (1.59% for object discrimination, 7.00% for face discrimination) seems to indicate that the PD group was disproportionately impaired for faces relative to objects, a ceiling effect on the object discrimination task may be acting to mask larger differences in overall object discrimination ability. The finding that either group showed any difference in performance between the two stimulus types was unexpected, given that no similar difference was observed in the pilot task. One possible explanation for this difference may be that the two types of stimuli used in this task were differentially susceptible to proactive interference, and that the interleaving of stimulus types in the pilot study facilitated a release from this proactive interference while the block design of Experiments 2a and 2b did not (However, see Experiment 3).

Aim 1 of the current study was to examine any effect of DA and dopaminergic medications on visual processing. While the face discrimination task provided no evidence of any effect of medication, the Group x Session interaction in the object discrimination task raised the possibility that the administration of levodopa had caused the PD group to perform worse in the afternoon that the morning. This is, in fact, the pattern of results predicted by Model 3 outlined above, in which levodopa causes an excess of DA that in turn causes dysfunction in the preserved DA circuitry of PD patients (see Section 1.6.3). However, the fact that no similar effect was observed in face discrimination makes this explanation somewhat problematic. Embracing the Dopamine Overdose Hypothesis in this instance would require either the assumption that excess DA was having differential effects on overlapping neural circuitry that was required for both tasks, which seems unlikely, or that excess DA disproportionately affected circuitry that was uniquely recruited for the face discrimination task. While

research indicating that face perception relies on specialized neural mechanisms (e.g., Kanwisher, McDermott, & Chun, 1997) seems compatible with the latter assumption, it is not obvious why there should be such differences in dopaminergic circuitry within a relatively small region of the temporal cortex. Failure to find any effect of session in Experiment 3 also casts doubt on a Dopamine Overdose explanation. In contrast, the fact that the PD group performed worse later in the day on a task for which they performed at or near ceiling in the morning adds to evidence from Experiment 1 that boredom or fatigue may have played a role in performance decrements in the Afternoon session. Indeed, one likely possibility is that what appears to be an interaction between group and session in the object discrimination results is actually separate effects of group and session, analogous to those observed in Experiment 1, but in this case the group effect for the morning session is masked by a ceiling effect.

The results of Experiments 2a and 2b are largely consistent with previous studies showing that individuals with PD tend to perform worse than their healthy counterparts at visual discrimination of complex visual stimuli. With respect to non-face objects, Laatu et al. (2004) showed that participants with PD were impaired relative to control participants at discriminating between line drawings of common objects and "scrambled" versions of those same objects in which features had been re-arranged. This finding in particular is suggestive of involvement by IT, since it is similar to some forms of apperceptive agnosia (see Section 6.1). With respect to faces, Levin et al. (1991) have previously showed that individuals with PD tend to perform worse than their healthy counterparts at the Benton Facial Recognition Test (BFRT), though there are several notable differences between the current task and the BFRT. In the BFRT, participants are simultaneously presented with a target photograph of one individual and an array of six test photographs: three that depict the same individual at angles other than the one used in the target photograph, and three that depict a different individual of similar appearance from various angles. Participants in this task are instructed to select the three test photographs that depict the individual in the target photo (Ducheine & Weidenfeld, 2003). The BFRT thus adds the requirement

that participants make discrimination judgements based on unseen perspectives of the person depicted, which may affect the cognitive demands of the task in unforeseeable ways. It is also notable that individuals completing the BFRT must make three correct judgments for each trial to be scored as correct, while Experiment 2b of the current study only requires one such judgment.

In contrast to the present study, Jacobs et al. (1995) found no difference between individuals with PD and healthy control participants in performance on the Facial Identity Discrimination task of the Florida Affect Battery-revised. The Facial Identity Task in the Florida Affect Battery-revised instructs participants to make a same/different judgment of two simultaneously presented photographs of faces, making it more procedurally similar to the current study. One possible explanation for the discrepancy in results is the incomplete masking of non-face cue in the Florida Affect Battery-revised, which is accomplished by using surgical caps to cover the hair of the individuals depicted. This procedure preserves the eyebrows and hairline of the subjects depicted in the task images, characteristics that have been shown to be sufficient for discrimination of face stimuli even when facial features are obscured (Ducheine & Weidenfeld, 2004). It is therefore possible that individuals with PD in Jacobs et al. (1995) were able to rely on non-face cues and bypass impaired face processing circuitry. By using 3-dimensional face stimuli that had been filtered to remove all non-face cues to identity, the task used in the present study required participants to make discrimination judgments solely on the basis of the structural features of face stimuli.

The mean difference between the two groups for these two tasks (1.58% for objects, 7.00% for faces) are still appreciably below the group difference observed in the pilot task (18.28%). It is therefore likely that differences observed between the PD group and the HOA group in the pilot study were driven by more than object and face discrimination deficits in members of the PD group. However, such deficits likely account for an appreciable portion of group difference in performance on the pilot task, and will have to be taken into account when interpreting Experiments 3 and 4.

Given the ceiling effects observed in both Experiment 1 and Experiment 2a, comparisons involving effect size for either task (let alone both) are likely to be misleading. However, it bears mentioning that while the mean difference between groups for Experiment 2b was greater than that of Experiment 1 (4.44%), the mean difference for Experiment 2a was not, so it is difficult to put much stock in this comparison. Consequently, while the group difference for the face discrimination task cannot be completely accounted for by the more basic feature discrimination deficits observed in Experiment 1, the same cannot be said conclusively of the object discrimination task. In other words, it is possible that the deficit in feature processing observed in the PD group for the line discrimination task may be sufficient to explain the lower performance by the PD group on the object discrimination task. The finding by Laatu et al. (2004) that individuals with PD performed worse than healthy individuals when discriminating drawings of familiar objects from scrambled versions of those drawings raises the possibility that individuals with PD may show impairment for the binding of features and not just the perception of these features themselves. It would be useful to know if errors made by participants with PD in this study were random or systematic. For instance, if participants were biased toward saying that drawings of objects were the same independent of the arrangement of their features, this could be taken as evidence that features were being accurately perceived, but the relationships among them were not, and that PD was thus disrupting processing at the whole-object level. However, this information was not reported by the authors.

Aim 2 of the present study was to examine the neural basis of visual impairments observed in individuals with PD. A major motivation behind Experiment 2 was to include tasks in this study that were known to recruit processing from IT in general and the fusiform gyrus in particular to see if these requirements led to a disproportionate drop in task performance by the PD group. This would have the effect of implicating IT as a weak link in ventral visual pathway-dependent processing. In addition to V1 and other early visual areas thought to be necessary for the performance of the line discrimination task

in Experiment 1, areas of IT have been shown to be necessary for the discrimination of complex objects and faces, such as those in Experiment 2 (Lehky & Tanaka, 2016). While the results of Experiment 2a fail to conclusively demonstrate the existence of object discrimination deficits beyond those resulting from more basic deficits of feature discrimination, to the extent that any individuals in the PD group showed disproportionately greater impairment in Experiment 2, it is reasonable to suspect that impaired IT processing could be responsible. This hypothesis is supported by a study of individuals with PD that correlated impaired performance on object perception tasks with grey matter loss in the cortex. Pereira et al. (2009) asked participants with PD and healthy control participants to complete the Benton visual form discrimination test (VFDT) as well as the BFRT, and grey matter volume was analyzed for each individual using MRI. The results of this study showed that, relative to their healthy counterparts, individuals with PD showed decreased grey matter density in regions of the frontal, parietal, and temporal lobes, as well as in several subcortical regions. Importantly for the current study, deficits in the BFRT task were associated with grey matter loss in the ventral occipitotemporal cortex, and the fusiform gyrus in particular. In contrast, performance deficits on the VFDT were associated with grey matter loss in visual association areas in bilateral superior parietal cortex. The fact that VFDT performance was not associated with IT processing may be related to the nature of the stimuli used in this task. The VFDT is a match-to-sample task in which the target stimulus consists of three simple geometric shapes, and distractors are generated by either moving, rotating, or distorting one of the three shapes (Campo & Morales, 2003). Discrimination in this task may thus depend on the spatial transformation of task stimuli, and the parietal areas identified by Periera et al. (2009) have indeed been associated with performance on location and spatial discrimination tasks (Haxby et al., 1991).

While Experiment 2a was intended as a test of the ability to visually discriminate complex objects, there was nothing in the design of this task that would have prevented participants from making their judgments by focusing on subsets of features in each figure without processing the figures

as a whole. Indeed, it would have been possible for participants to base their judgments on single segments of each figure, making the stimuli in this task, in effect, noisier versions of the line stimuli in Experiment 1. This is largely a result of the way the study was developed, since the tube sculpture figures were used in the pilot study before it became apparent that a control task, such as line discrimination, would be prudent. However, it was also not obvious *a priori* whether or not participants would choose to adopt a feature-based task strategy for the object discrimination task. Further, it was not clear that participants would even be able to employ such a strategy if PD or levodopa produced a perceptual deficit for complex objects, since the ability to identify corresponding segments between different stimulus figures for comparison necessitates some minimal understanding of the relationship between individual segments and the larger figures. For example, it would be difficult to "cheat" on this task by only comparing only the "end" tubes of each figure if one could not perceive the sculptures as having discernible ends in the first place. So, despite some perceptual overlap with the stimuli in Experiment 1, the object discrimination task had the potential to provide instructive observations: Any pattern of results would indicate whether or not individuals could successfully differentiate the different stimuli in each experiment, but in the case where an individual did well on both tasks, it could not be ruled out that successful performance on complex object discrimination was the result of a feature-based discrimination strategy. In any case, the difficulty in comparing results across Experiments 1 and 2a that arose from the ceiling effects on both means that questions of strategy cannot be resolved on the basis of the data collected.

In summary, the results of Experiment 2 support the existence of face discrimination deficits in individuals with PD, and previous studies have suggested grey matter atrophy in ventral visual pathway structures as a possible cause. Failure to find any effect of DA manipulation in Experiment 2 is consistent with the proposed mechanisms. However, further research is required to establish the existence of, and

any neural underpinnings for, deficits in non-face object discrimination beyond those of simple feature discrimination in individuals with PD.

CHAPTER 7: EXPERIMENT 3

7.1 Background

Experiments 3 and 4 address the functionality of pathways projecting from IT to other areas of the brain involved in complex visual tasks. Specifically, Experiment 3 examines changes in the ability of individuals with PD to maintain visual representations over a brief delay, which is thought to involve a complex interplay between IT and the PFC.

The roles that these two areas play in VWM is still a matter of considerable debate. The sensory recruitment model posits that the contents of working memory are a result of reactivation of the sensory cortices involved in the encoding of the relevant representations, and the role of the PFC is largely to supervise the process of reactivation (Gayet, Paffen, & Van der Stigchel, 2018; Scimeca, Kiyonaga, & D'Esposito, 2018). An opposing view, advanced by Xu (2017), is that the representations that form the contents of working memory are principally stored in PFC, with visual sensory cortices being nonessential (Xu, 2017). Other accounts are notably more nuanced. For instance, Courtney et al. (1997) conducted an fMRI study of human participants performing a working memory task using faces as stimuli and found multiple areas in both ventral occipitotemporal cortex and PFC where activity was modulated by the task. Of the three areas identified in the visual cortex, the two located more anteriorly showed activity that was not only sustained over a delay, but which was also preferentially activated by face stimuli as opposed to control stimuli. The three areas identified in PFC displayed a spectrum of response properties, with posterior middle frontal cortex producing disproportionately transient activation in response to visual stimuli in the task with minimal sustained activation, the anterior middle frontal cortex showing the opposite pattern, and the inferior frontal cortex displaying intermediate levels of both transient and sustained activations. This pattern is interpreted by the authors as indicating that both ventral occipitotemporal cortex and PFC contain hierarchies of processing including both

sensory processing and working memory maintenance. In other words, visual working memory is the result of both cortical areas working in concert at a variety of processing levels.

Additionally, studies of VWM in monkeys have identified cells that exhibit sustained activation during delay intervals that is selective for object identity. Rao, Rainer, and Miller (1997) recorded from neurons in the lateral PFC of monkeys and found cells that responded selectively to a remembered object during a memory delay, as well as cells whose activity was driven by both object identity and object location. These findings were replicated by Rainer, Asaad, and Miller (1998), and Courtney et al. (1996) have used positron emission tomography with human participants and identified areas in lateral PFC that were selectively activated by faces in a VWM task, independent of their location. While these studies cannot speak to the richness of visual representations in the PFC, and there has been no suggestion to date that such representations are retinotopically organized as they are in IT or other areas of the ventral visual pathway, it does seem plausible that information pertaining to object identity is represented in PFC above and beyond what is needed to reactivate the relevant areas of visual cortex. Further, while both PFC and IT in monkeys have been shown to maintain stimulus-selective information over delays, only in PFC is this activity maintained following the presentation of new visual stimuli to which the animals are required to attend (Miller, Erickson, & Desimone, 1996).

7.2 Methods

7.2.1 Participants

All participants from the study sample completed this experiment and were included in the analysis. See section 3.3 for details concerning sample characteristics and recruitment methods.

7.2.2 Stimuli

The face and object stimuli used in this task were generated by the same methods used in Experiments 2a and 2b, as well as the Pilot study. However, a new set of these stimuli were created for

this experiment, such that no face or tube sculpture was reused across tasks or sessions. See sections 6.2.2 and 6.4.2 for a complete description of these stimuli.

7.2.3 Procedure

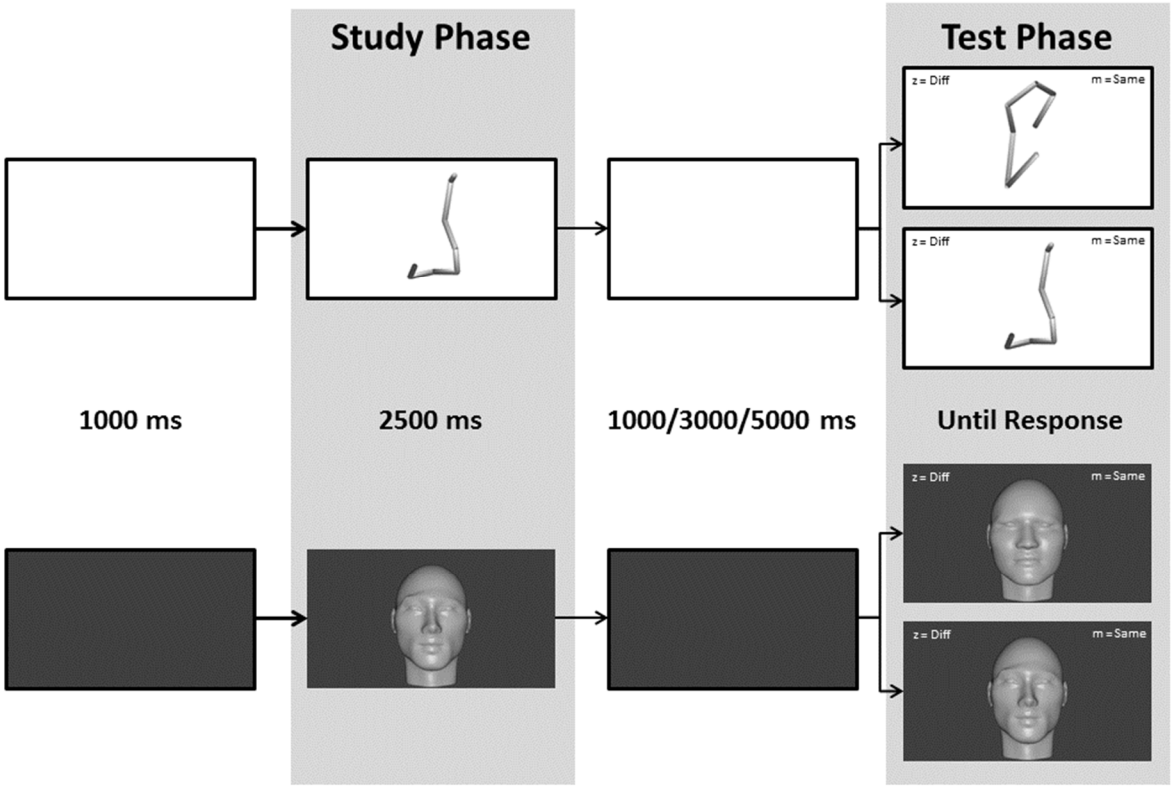


Figure 20. Trial procedure for the visual working memory task. Stimuli were the same as those used in Experiments 2a and 2b, as well as the Pilot study.

This task was composed of 72 trials. Each trial in this task comprised a Study period and a Test period. During the Study period (2500 ms), participants were asked to study and remember an object or face presented on the screen. The Study period was followed by one of the three designated delay intervals. While the delay in the Pilot study was a constant 3000 ms, in Experiment 3 only one-third of the trials had a 3000 ms delay, while another one-third had a 1000 ms delay, and another third had a 5000 ms delay. The delay was followed by a Test period in which participants were asked to indicate whether an object or face that subsequently appeared on the screen was the same as or different than the object presented in the Study period. In contrast to the pilot study, in Experiment 3, stimuli that

were the same were always presented at the same angle during Study and Test periods. Half of all participants were instructed to respond by pressing "z" if they believed the object or face was the same and "m" if the object or face was different, while the other half of participants were assigned the reverse key mapping. There was no pre-set time limit on each trial, so the stimuli remained on the screen until the participants responded. The task was delivered in four equal-sized blocks, between which the experiment paused, informed participants of their progress, and encouraged them to take a break for as long as they liked prior to resuming.

7.3 Results

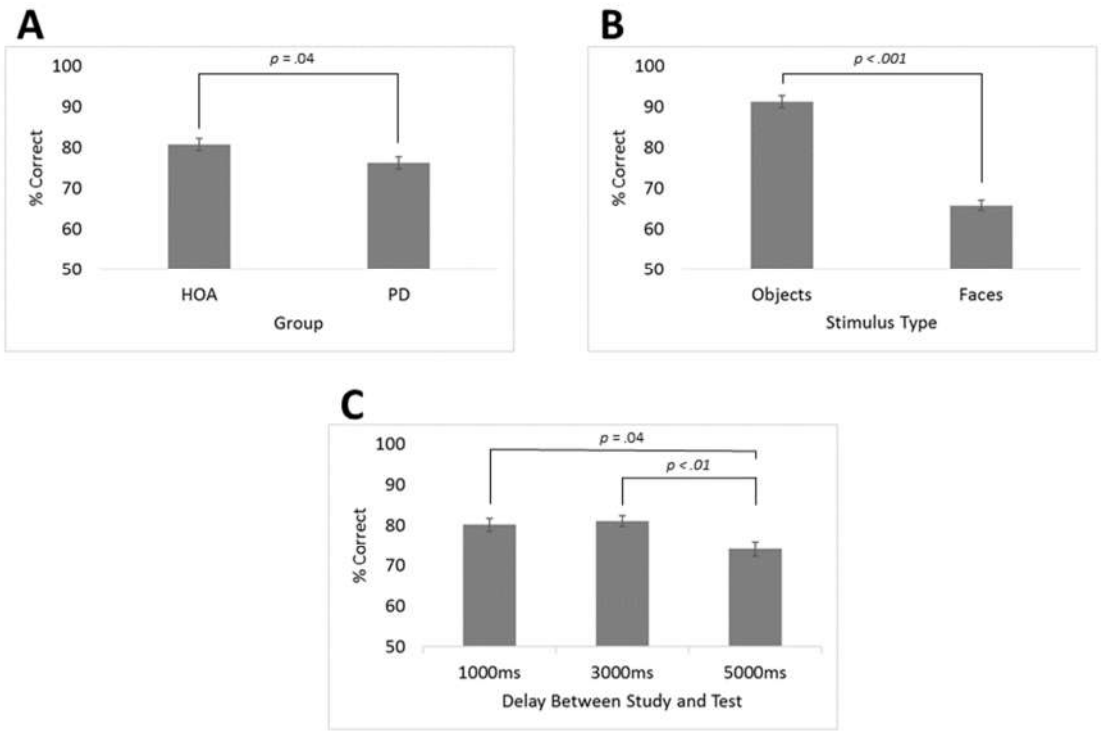


Figure 21. Significant effects from the visual working memory task. A: Main effect of Group. B: Main effect of Stimulus Type. C: Main effect of Delay. Error bars represent standard errors.

The effect of PD pathology and levodopa treatment on VWM were examined using a 2 (Group: PD vs. HOA) x 2 (Session: Morning vs. Afternoon) x 2 (Stimulus Type: Objects vs. Faces) x 3 (Delay: 1000, 3000, and 5000ms) mixed factorial ANOVA. The results showed a main effect of Group, $F(1,26) = 4.62$, $p = .04$, $\eta^2_p = .151$, with the HOA group (M = 80.75%, S.E. = 1.50%) scoring higher than the PD group (M =

76.19%, S.E. = 1.50%). There was also a main effect of Stimulus Type, $F(1,26) = 224.20$, $p < .001$, $\eta^2_p = .896$, with participants across groups performing better on Object trials (M = 91.17%, S.E. = 1.47%) than Face trials (M = 65.77%, S.E. = 1.24%), as well as a main effect of Delay, $F(2,52) = 6.98$, $p < .01$, $\eta^2_p = .212$, with participants across groups performing better on both the 1000ms delay trials (M = 80.21%, S.E. = 1.57%) and 3000ms delay trials (M = 81.10%, S.E. = 1.30%) than on the 5000ms delay trials (M = 74.11%, S.E. = 1.84%). No other effects or interactions were significant.

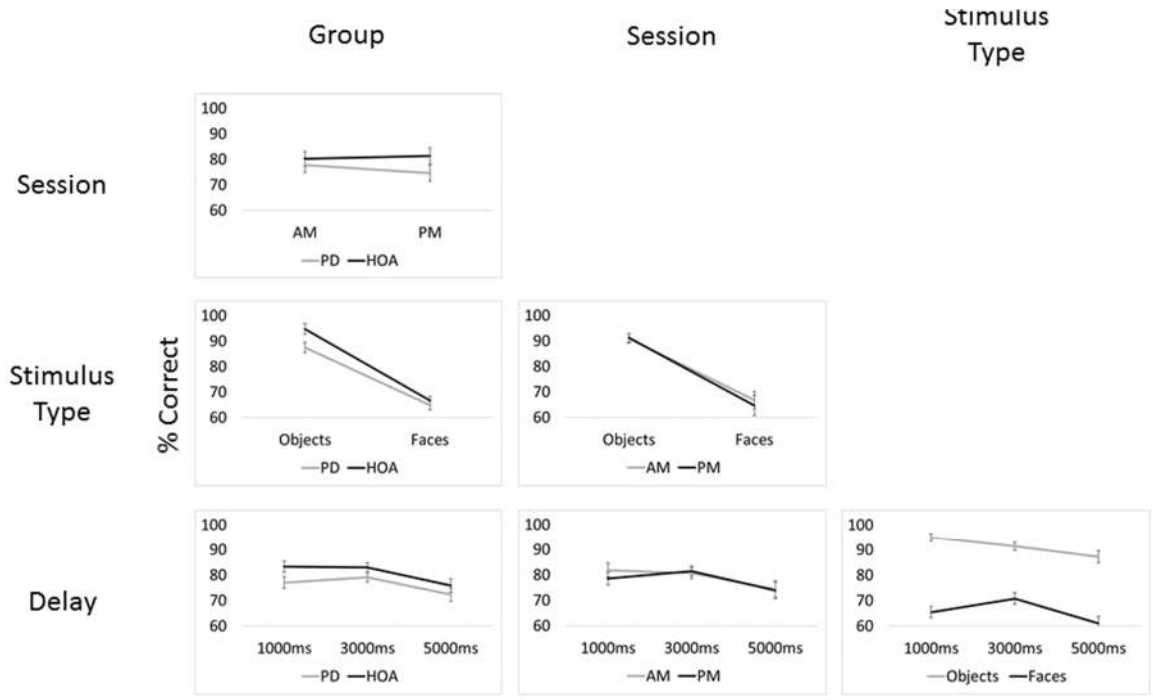


Figure 22. Non-significant two-way interactions from Experiment 3. Error bars represent standard errors.

The relationship between levodopa administration and task performance for individuals in the PD group was also assessed by calculating difference scores for the VWM task and the motor portion of the UPDRS between sessions and performing a correlational analysis. The correlation did not reach significance either when all participants were analyzed ($p = .71$) or when participants whose UPDRS motor scores did not improve for the afternoon session were removed ($p = .43$). Overall performance by the PD group during the Afternoon session was again examined for a relationship with PD progression.

No relationship was observed between task performance and either UPDRS scores (p = .45) or years since disease onset (p = .90).

7.4 Discussion

Experiment 3 was designed largely as a replication of the pilot study, absent the now defunct stimulus rotation manipulation. Accordingly, the results again demonstrated that individuals with PD tend to be worse than their healthy counterparts at tasks that require maintaining visual representations over a delay. While the group effect itself remained, it is notable that the difference in group means in Experiment 3 (4.56%) was appreciably smaller than that of the pilot study (18.28%). Given the difference between the two studies, several factors may account for this rather large discrepancy. First, the narrowed age range for the main study resulted in the exclusion of primarily older individuals. This may have not only reduced the variability in task performance due to age-related cognitive decline, but also excluded participants from the PD group with longer disease durations and thus greater disease-related deficits. Consistent with this latter point, it can be seen that the scores for the PD groups rose appreciably in the main study (66.41% in the pilot study vs. 76.19% in Experiment 3) while the HOA groups were closer between studies (84.69% in the pilot study vs. 80.75% in Experiment 3). Second, the larger sample in the main study meant that there was less of an opportunity for more extreme scores to overly influence the group average. Additionally, it is possible that the refinements implemented in the study design (displaying the key mappings on the screen, adding an acclimation task, adding breaks to the task procedures) disproportionately advantaged individuals in the PD group. Within-task breaks were likely particularly helpful given that increased fatigue is a common symptom of Parkinson's disease, with clinically significant fatigue observed in 33-58% of disease sufferers, depending on the study (Friedman et al., 2006). Thus, the effect of group in the present experiment likely represents a more valid measurement of the effects of PD on VWM task performance.

The effect of stimulus type was larger in Experiment 3 than either Experiment 2 or the pilot study. While the effect in Experiment 2 may have been reduced by a ceiling effect for the object recognition task, the same cannot be said for the pilot task. In the discussion for Experiment 2, the researcher speculated that the reason for the discrepancy might have been due to a buildup of proactive interference for faces in Experiment 2, since the pilot study prevented such an issue by interleaving face and object trials. However, in Experiment 3, the order of the two stimulus trial types was randomized. Accordingly, if proactive interference had been the whole story behind the effect of stimulus type, then the size of the effect for Experiment 3 should have been somewhere in between that in Experiment 2 and the pilot study, which was not the case. It cannot be that the delay in Experiment 3 somehow exacerbated the effect of stimulus type in Experiment 2, because a retention interval was also present in the pilot study, which showed no effect of stimulus type. So while the results of Experiments 2 and 3 provide strong evidence that individuals in both groups were more proficient at discriminating the abstract object stimuli than the face stimuli used in this study, it is unclear what factors are driving the magnitude of this difference across tasks.

Aim 1 of the current study was to examine any effect of DA and dopaminergic medications on visual processing. No effect of session was observed for this experiment, either as a main effect or an interaction. This observation supports the conclusion that levodopa administration has no appreciable effect on performance of VWM tasks by individuals with PD.

The mean difference between the two groups in Experiment 3 (4.46%) fell between the mean differences for the object discrimination (1.58%) and face discrimination (7.00%) tasks in Experiment 2. This observation is consistent with the idea that the group effect for the VWM task could be explained in large part by the comparatively lower performance of the PD group in discriminating the stimuli themselves, absent any effect of difference in working memory ability. The main effect of delay observed in Experiment 3 indicates that the manipulation of retention interval used was sufficient to

modulate the accuracy of participants' judgments. However, no interaction was observed between group and delay that might have indicated that the PD group was disproportionately affected by the working memory aspect of this task. As a result, it is unclear from the present study to what extent the main effect of group can be explained by deficits in VWM.

Aim 2 of the present study was to examine the neural basis of visual impairments observed in individuals with PD. A major motivation behind Experiment 3 was to include a task in this study that was known to recruit processing from the PFC to see if this requirement led to a disproportionate drop in task performance by the PD group. This would have the effect of implicating the PFC as a weak link in ventral visual pathway-dependent processing. However, the results of the current study are not sufficient to tease apart to relative contribution of PFC -dependent VWM and ventral pathway-dependent perceptual discrimination impairments to diminished performance on this task. Other research suggests that the PFC is necessary for the maintenance of visual representations of unseen stimuli in both monkeys (Miller, Erickson, & Desimone, 1996) and humans (Haxby et al., 2000; Courtney et al., 1997), and that PD is associated with pathology of the frontal lobe (Double et al., 1996). Likewise, behavioral research has indicated that individuals with PD show impairment on PFC-dependent tasks, even relatively early in the course of the disease (Muslimović et al., 2005; Cools et al., 2003). Further research should be conducted to investigate whether impairments to VWM observed in individuals with PD, such as the one reported here, are associated with neurological degeneration of the PFC.

Experiment 4 will again examine deficits in PD for tasks associated with frontal lobe function, but within the context of mental transformation of visual representations rather than their maintenance.

CHAPTER 8: EXPERIMENT 4

8.1 Background

Mental rotation can be conceptualized as an extension of VWM in that it requires the maintenance of visual representations in the brain, but with the additional requirement of manipulating those representations in a goal-directed fashion. Predictably then, mental rotation has been shown to employ the ventral visual pathway, which is involved in processing of objects, and frontal areas involved in the maintenance of working memory, as discussed above. However, this task also involves the interface between the ventral and dorsal visual pathways and, of particular interest in a study examining PD pathology, several motor areas of the brain. With respect to the visual areas discussed previously in this study, imaging studies have shown the primary visual cortex to be active during mental rotation tasks (Jordan et al., 2001), as well as bilateral extrastriate areas (Tagaris et al., 1997, Zacks 2008) and IT in particular (Jordan et al., 2001). Additionally, imaging studies show areas in the frontal lobe to be active during mental rotation tasks. This includes regions of the right superior, middle, and inferior frontal gyri (Jordan et al., 2001; Tagaris et al., 1997), as well as bilateral PFC (Zacks, 2008; Cohen et al., 1996).

Briefly, the dorsal visual pathway emerges from the primary visual cortex of the brain and travels anteriorly via a more dorsal route, as its name would suggest. This pathway is disproportionately involved in spatial processing, and the constituent region with the highest level of processing is commonly considered to be the posterior parietal cortex (PPC), which surrounds the intraparietal sulcus (Janssen, Verhoef, & Premereur, 2018). The PPC is functionally divided into cortical areas that appear to be organized around “effectors”, such that the medial intraparietal and anterior intraparietal areas whose activity is associated with reaching and grasping movements (respectively), and lateral intraparietal area whose activity is associated with visual saccades. Notably, activity in the caudal intraparietal area has been implicated in tasks requiring three-dimensional visual processing (Katsuyama

et al., 2010). Imaging studies of participants completing mental rotation tasks have identified task-related activations in bilateral PPC (Christophel et al., 2015; Cohen et al., 1996), particularly in the areas of the intraparietal sulcus (Zacks, 2008; Jordan et al., 2001) and the superior parietal lobule (Tagaris et al., 1997).

That the mental manipulation of objects in space involves areas with known roles in object and spatial processing, as well as working memory and executive functions, is perhaps not terribly surprising, and pathways have been identified between these areas that could support a functional interface (Janssen et al., 2018, Amick et al., 2006; Middleton & Strick, 2000). Less clear is the role of motor regions in mental rotation, where task-relevant activity has also been identified (Zacks, 2008; Jordan et al., 2001; Tagaris et al., 1997). Several transcranial magnetic stimulation (TMS) studies have been conducted examining this question, but the results have not lent themselves to straightforward interpretation. For instance, a study by Cona, Marino, and Semenza (2017b) applied short trains of pulses over the supplementary motor area (SMA) and primary motor cortex (M1) at 350 ms following the visual presentation of pairs of abstract objects and hands. The SMA has been implicated in the planning of and preparation for complex movements (Ohara et al., 2000), while M1 has been implicated in the execution of movements and movement sequences (Karni et al., 1998), In the study, participants were asked to judge whether the stimulus pairs were the same or mirror images of one another, and the stimuli could be rotated in depth with respect to one another at either 0, 50, 100, or 150 degrees. The researchers reported that tetanic stimulation over the SMA reduced the number of errors that participants made on the task at higher angles of rotation (i.e., 100 and 150 degrees), but only when the stimuli compared were abstract objects and not hands. However, while the same train of TMS stimulation over M1 produced no significant changes in rotation performance in that study, a different study by Ganis et al. (2000) found that a single pulse of TMS administered to M1 at 650 ms post-stimulus increased error rates for individuals performing mental rotation of hand and foot stimuli, but only for one of the four

rotation angles used (60 degrees out of 20, 60, 100, and 140 degrees). Another study by Cona, Marino, and Semenza (2017a) used TMS over the dorsal premotor cortex (PMd) of individuals performing mental rotations on pairs of objects and hands and found that TMS impaired accuracy in the mental rotation of objects, but only on trials where the correct response was “same”. Activations of the PMd have been associated with the planning and visual guidance of movements (Cisek & Kalaska, 2005).

Some researchers have suggested that any visual object that the brain registers as graspable automatically primes mental representations of motor actions related to that object (Grèzes & Decety, 2001). On this account, activity observed in motor areas during mental rotation is an epiphenomenon and should show no strong association with task performance. Other researchers have argued that SMA and PMd, though commonly identified principally as motor regions, actually subserve domain-general processing. For instance, Cona and Semenza (2017) posit that the SMA is involved in sequence processing for a broad array of cognitive tasks involving timing, numerical cognition, working memory, language, music perception/production, and spatial processing. In support, the authors cite studies showing that SMA activity increases with the duration of synchronization-continuation tapping tasks (Crowe et al., 2014), the amount of angular rotation in mental rotation tasks (Milivojevic, Hamm, & Corballis, 2009), the number of operands in an arithmetic problem (Menon et al., 2000), and the complexity of improvisations produced by musicians (Bengtsson, Csikszentmihalyi, & Ullén, 2007). They also note that damage to the SMA has been shown to cause dysfluent speech (Ziegler, Killan, & Dieger, 1997), deficits in producing sequential memory-guided saccades (Gaymard, Pierrot-Deseilligny, & Rivand, 1990), and varying degrees of akinesia (Potgieser et al., 2014). While a subset of the examples cited by Cona and Semenza (2017) seem as though they could be equally well explained by a more general role for SMA in working memory, the authors also refer to several single-unit recording studies of the SMA in monkeys that identified cells with sequence-specific response properties, such as coding the specific order of a task in a larger sequence (e.g., a cell active up to the third movement in a series),

and cells that responded specifically to either even- or odd-numbered events in a series (Shima & Tanji, 2000).

In a similar vein, Ptak, Schnider, and Fellrath (2017) have proposed that the PMd and the superior parietal cortex form a network that facilitates emulations of actions and movements, irrespective of the effector. The authors refer to this network as the dorsal frontoparietal network (dFPN) and characterize its activity as creating a dynamic representation of objects and movements in space for the purposes of manipulation, prediction, and online error. As evidence, they point to research indicating a high degree of overlap in activations across dFPN between imagined and executed actions, as well as studies showing motor compatibility effects such as interference between imagined movements and actual movements that are incompatible in real space (ctd. in Ptak, Schnider & Fellrath, 2017). Both of these latter models offer plausible – and not mutually exclusive – explanations for the recruitment of nominally motor areas during mental rotation tasks that require the manipulation of mental representations into orientations not available through direct perception. Neither the sequence processing nor the dFPN model posits an explanation for research showing M1 recruitment in mental rotation tasks.

The current experiment is not designed to adjudicate on these competing explanations, since they only predict that motor areas will be recruited during mental rotation. However, this processing demand, if it exists, is unique among experiments in the current study, such that a disproportionately large performance deficit by the PD group on this task would provide evidence that the motor areas themselves, and not upstream visual processing, are responsible for mental rotation impairments observed in PD.

8.2 Methods

8.2.1 Participants

Following completion of this task, one participant in the PD group asked several questions that gave a strong impression that this individual had not completely understood or followed the instructions for this experiment. When asked more directly if this individual felt they had performed the task correctly the individual replied that they had. However, given the uncertainty on the part of the experimenter, and out of an abundance of caution, this participant's data, as well was that of their matched control, were omitted from further analysis for this task. All other participants from the study sample completed this experiment and were included in the analysis. See section 3.3 for details concerning sample characteristics and recruitment methods.

8.2.2 Stimuli

Because the rotation manipulation in the pilot study was unsuccessful in producing an observable disruption in stimulus processing, this experiment was designed to more closely resemble a study by Lee et al. (1998) in which an effect of angular rotation on task performance was observed. To this end, the stimuli used were a set of perspective line drawings of novel 3-dimensional objects. This stimulus set was developed by Ganis and Kievit (2015) as an update to a classic stimulus set developed by Shepard and Metzler (1971). The objects consisted of 7-11 cubes serially connected face-to-face in such a way that four 90-degree angles were formed along the length of the object. On each trial, two of the line objects were simultaneously presented on the screen, aligned horizontally. On half of all trials, both stimuli had the same structural description, while on the other half one of the four angles were changed in orientation to slightly alter the figure. Further, stimuli were rotated with respect to one another by either 0, 50, 100, or 150 degrees about the Y-axis.

8.2.3 Procedure

This task was composed of 36 trials. Each trial began with a blank screen that persisted for one second, followed by the simultaneous presentation of two horizontally aligned object stimuli. Half of all participants were instructed to press the "z" key if they believed that the two stimuli were the same and the "m" key if they believed the stimuli were different, while the other half were instructed to use the reverse key mapping. There was no pre-set time limit on each trial, so the stimuli remained on the screen until the participants responded. The task was delivered in four equal-sized blocks, between which the experiment paused, informed participants of their progress, and encouraged them to take a break for as long as they liked prior to resuming.

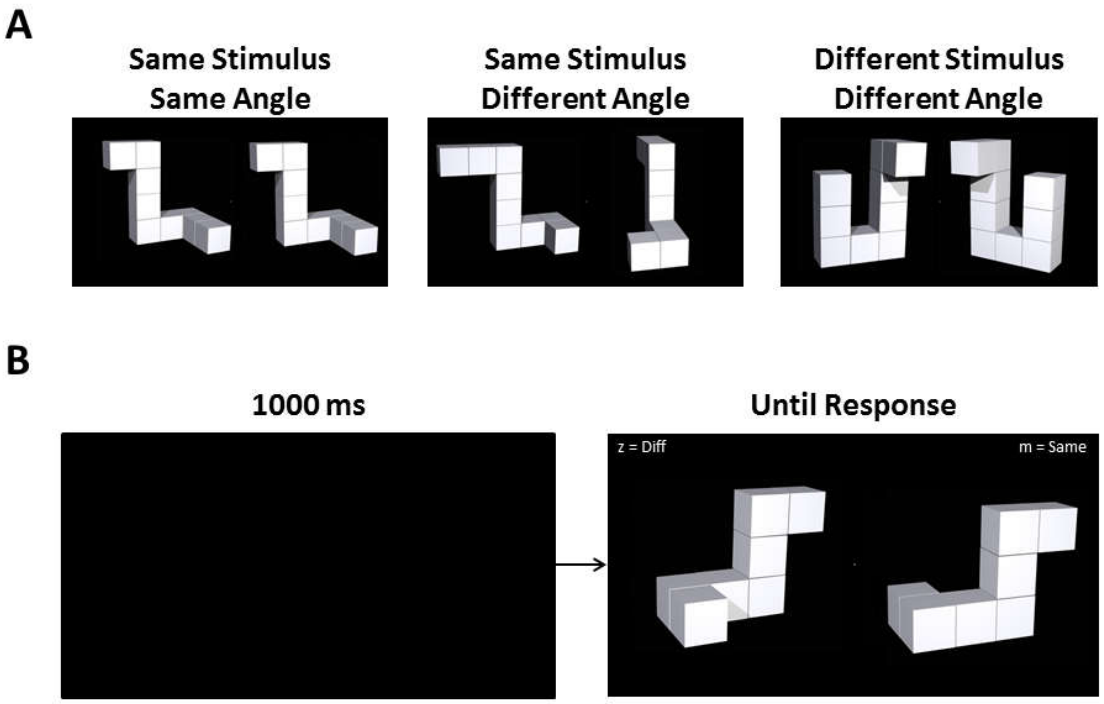


Figure 23. A: sample stimuli and B: trial sequence for Experiment 4. This stimulus set was developed by Ganis and Kievit (2015). Angles between stimuli were either 0, 50, 100, or 150 degrees. Rotation is about the y-axis.

8.3 Results

This experimental task is in large part a replication of Lee et al. (1998). Among other findings, these authors reported that some of the effects in their analyses were mediated by whether the

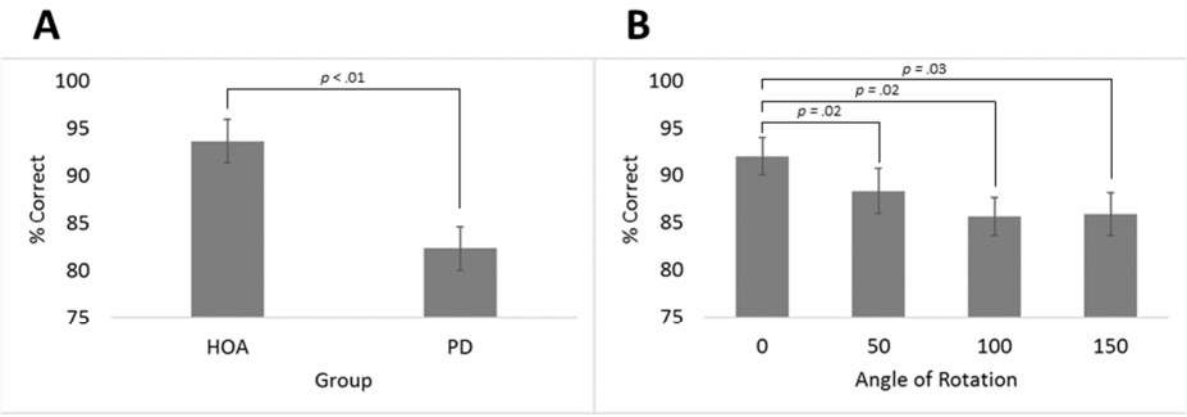


Figure 24. Significant effects from the object rotation task. A: Main effect of Group. B: Main effect of Angle. Error bars represent standard errors.

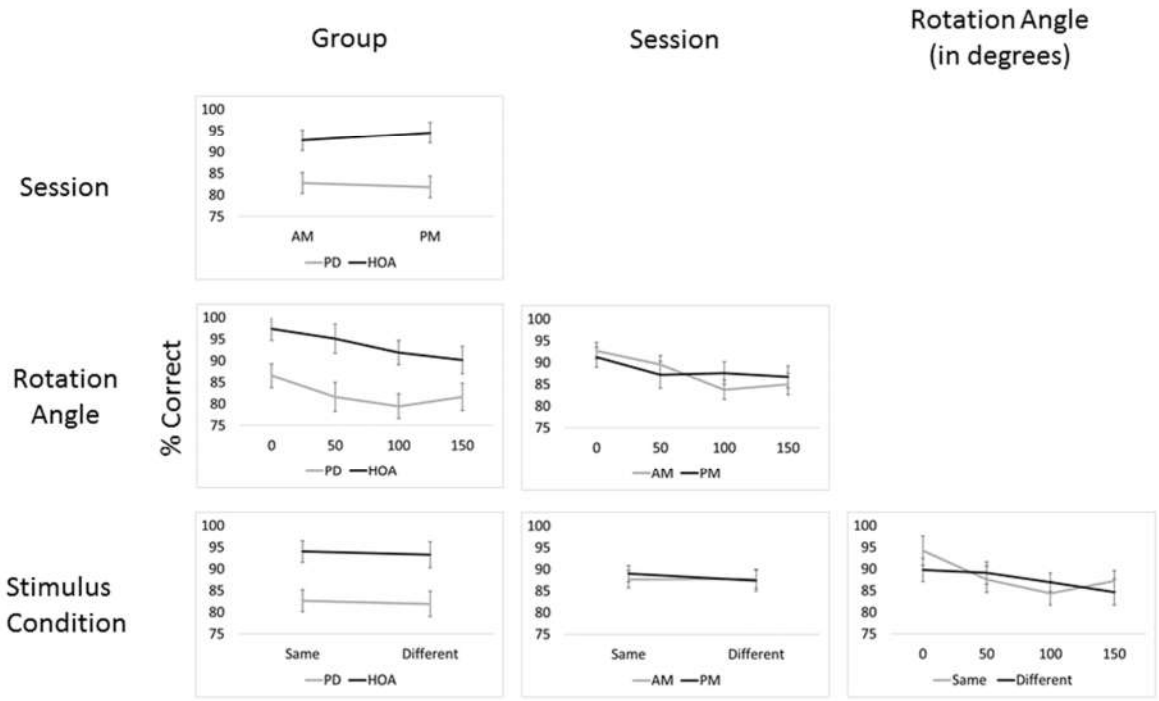


Figure 25. Non-significant two-way interactions from Experiment 4. Error bars represent standard errors.

abstract objects were the same or different during stimulus presentation. As such, the present analysis examined the role of Same vs. Different on participants' task scores. The effects of PD pathology and levodopa treatment on mental rotation were thus examined using a 2 (Group: PD vs. HOA) x 2 (Session: Morning vs. Afternoon) x 2 (Identity: Same vs. Different) x 4 (Angle: 0, 50, 100, and 150) mixed factorial ANOVA. There was a main effect of Group, $F(1,24) = 12.043$, $p < .01$, $\eta^2_p = .334$, with the HOA group

making more correct judgments (M = 93.63%, S.E. = 2.31%) than the PD group (M = 82.32%, S.E. = 2.31%). There was also a main effect of rotation angle, $F(3,72) = 3.25$, $p = .03$, $\eta^2_p = .119$, with both groups performing better on trials with 0° of rotation (M = 91.99%, S.E. = 1.96%) than trials with 50° (M = 88.36%, S.E. = 2.38%), 100° (M = 85.68%, S.E. = 2.00%), or 150° (M = 85.90%, S.E. = 2.26%) of angular rotation. No other effects or interactions rose to the level of significance.

The relationship between levodopa administration and task performance for individuals in the PD group was also assessed by calculating difference scores for the mental rotation task and the motor portion of the UPDRS between sessions and performing a correlational analysis. The correlation did not reach significance either when all participants were analyzed ($p = .63$) or when participants whose UPDRS motor scores did not improve for the afternoon session were removed ($p = .32$). Overall performance by the PD group during the Afternoon session was again examined for a relationship with PD progression. No relationship was observed between task performance and either UPDRS scores ($p = .17$) or years since disease onset ($p = .22$).

8.4 Discussion

The results of Experiment 4 are consistent with the finding by Lee et al. (1998) that individuals with PD are impaired at mental rotation relative to their healthy counterparts. Indeed, the mean difference observed between the two groups in this study (11.31%) was the largest observed in any of the five experiments in this study. This observation is particularly striking given that this was not the most difficult of the five experimental tasks, as judged by the performance of the HOA group, which served as a baseline for this study. This finding raises the possibility that the impairment observed for the PD group in this task may be of a qualitatively different nature than those observed for the first four tasks, and that one or more of the unique processing requirements of this task disproportionately disadvantaged the PD group.

The main effect of angle observed in the present study indicates that the rotation manipulation was sufficient to disrupt discrimination judgments for the object rotation task. However, both groups appear to have been similarly affected, as there was no interaction between angle and group. This lack of interaction is at odds with the findings of Lee and colleagues. In their study, Lee et al. (1998) found that their PD group was disproportionately impaired at the highest angles of stimulus rotation when the two stimuli were the same. In particular, when stimuli were rotated more than 120° in depth, the PD group in that study actually performed worse than chance, indicating that they had adopted a maladaptive strategy for making their discrimination judgments. In contrast, individuals with PD in the present study were still averaging 80.77% correct for the same trial type.

Several factors may account for this difference in results. The sample size for the current study was almost twice the size used by Lee and colleagues, making it less likely that results would be unduly influenced by one or two individuals using a counterproductive task strategy. Perhaps more significantly, the stimulus set used in the present study differed from that used by Lee et al. in the way that "different" stimuli were generated. Specifically, Lee et al. used the traditional Shepard and Metzler (1971)-type stimuli where objects in the "different" condition were all mirror images of one another. In contrast, the present study used stimulus set developed by Ganis and Kievit (2015) where objects in the "different" condition were "pseudo-mirror" images of one another, and therefore not always chiral (Ganis & Kievit, 2015, pg. 2). The inclusion of these non-chiral stimuli may have been sufficient to disrupt the adoption of whatever maladaptive strategy produced the interaction in Lee et al. (1998).

Aim 1 of the current study was to examine any effect of DA and dopaminergic medications on visual processing. No effect of session was observed for this experiment, either as a main effect or an interaction. This observation supports the conclusion that the manipulation of DA levels in the brain has no appreciable effect on performance of mental rotation tasks by individuals with PD.

It is worth noting that not all mental transformations of objects have been observed to be disrupted in PD, and the 3D manipulation of objects used in this study may be an exception rather than the rule. For instance, the pilot task in this study required participants to mentally transform 3D stimuli by rotating them to unseen perspectives, but this manipulation produced no appreciable group difference in accuracy. In that task, the smaller angles of rotation resulted in a comparatively smaller disruption in the spatial relationships among features, so this difference in results may simply have been one of degree. However, Lee et al. (1998) also included a task that required participants with and without PD to make discriminations of Shepard and Metzler stimuli that were rotated within the picture plane, instead of in depth. Stimuli in this task were rotated by the same angles as used in the depth rotation task, but the researchers observed no difference in accuracy between groups. Similarly, Ogden, Growdon, and Corkin (1990) administered the Spatial Relations task of the Differential Aptitude Test to individuals with PD and healthy control participants, a task that requires participants to match a target stimulus with a picture of what that stimulus would look like if folded along an indicated axis. These researchers similarly observed no difference in accuracy between groups. It may therefore be some processing demand unique to mental rotation at large angles in depth that is impaired in individuals with PD, rather than a more general deficit in the mental transformation of objects.

Aim 2 of the present study was to examine the neural basis of visual impairments observed in individuals with PD. Of all the tasks administered in the present study, the results of the mental rotation task in Experiment 4 seem to represent the best case for a group difference that represents a domain-specific impairment. That is, this task produced the largest mean difference in accuracy between groups despite its not being the most difficult task, as indicated by the performance of the HOA group. Any brain region uniquely recruited for this experimental task would therefore be a candidate weak link in ventral stream-dependent processing.

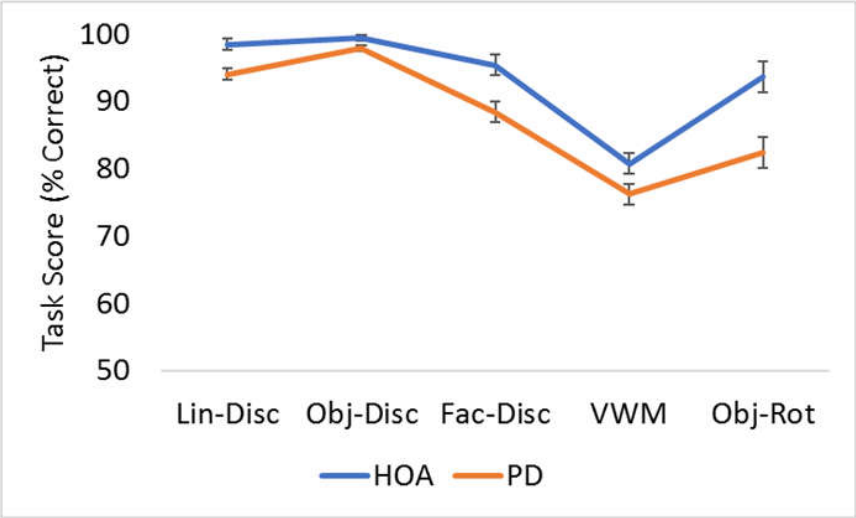


Figure 26. Scores across tasks for both groups. Error bars represent standard errors.

Mental rotation is notable for its reliance on processing in the PFC. Cohen et al. (1996) used fMRI to examine the brains of healthy participants and observed activation in dorsolateral PFC (Brodmann areas 9 and/or 46) in half the individuals tested while performing a mental rotation task using Shepard and Metzler stimuli. Further, a meta-analysis of mental rotation studies by Zacks (2008) documented seven other studies where mental rotation had produced above-threshold activations in the PFC, and traced their overlapping activations to the inferior frontal cortex (Brodmann areas 44 and 45). However, VWM is also associated with PFC activations. A study by Courtney et al. (1997) used fMRI to examine brain activity associated with working memory for faces and identified three prefrontal regions with task-driven sustained activations: inferior frontal gyrus, posterior middle frontal gyrus, and anterior middle frontal gyrus. Processing in PPC is another hallmark of mental rotation. The same study by Cohen et al. (1996) that identified PFC activation during mental rotation also found widely distributed task-driven activity in PPC (Brodmann areas 7a and b) across all participants, while a study by Jordan et al. (2001) found consistent activation within the intraparietal sulcus while participants performed mental rotations of a variety of stimuli, including Shepard and Metzler-type 3D stimuli. However, the PPC (in particular the angular gyrus and the posterior supramarginal gyrus) is also the area most strongly associated with performance deficits on the BLO test (Tranel et al., 2009). While further research is

required to determine the precise extent to which these various task activations coincide, it is at least not obvious based on these various findings that either PFC or PPC areas were uniquely recruited for Experiment 4. By extension, neither PFC nor PPC damage in individuals with PD provides a conclusive explanation for the larger mean difference in accuracy observed for Experiment 4, though both possibilities warrant further investigation.

If the poor performance by the PD group on the mental rotation task indeed represents a qualitatively different processing impairment than has been observed for the other experimental tasks, the research discussed thus far would make impairment in motor regions a likely target for investigation. Significant task-driven activations in motor areas have been identified in other studies of mental rotation using similar stimuli. The meta-analysis of mental rotation experiments by Zacks (2008) identified the precentral sulcus as a common site of task-relevant activation during mental rotation. Areas in the region identified included the SMA, as well as portions of M1 and the lateral premotor cortex. These are areas where processing is known to be impaired in individuals with PD. Specifically, PD is associated with decreased activity in the SMA and increased activity in M1 compared with healthy individuals of similar age (Haslinger et al., 2001; Rascol et al., 1994; Jenkins et al., 1992), and altered signaling between these areas and other areas with which they are connected (Wu et al., 2009). This abnormal activity has been shown to be correlated with motor symptoms in PD, with depressed SMA activity in particular being associated with akinesia and tremor (Ng et al., 2017; Jenkins et al., 1992). Further, mild cognitive impairment and dementia in the later stages of the disease have been associated with grey matter hypometabolism and atrophy in the SMA and other precentral motor areas (González-Redondo et al., 2014). Thus, not only is motor cortical pathology a signature of PD, but this pathology has been linked to overt behavioral effects, as well as cognitive effects in more advanced PD.

If models that characterize supplementary and premotor cortical areas as subserving spatial transformation (Cona & Semenza, 2017) and action emulation (Ptak et al., 2017) prove accurate, then it

would not be surprising to find that pathology affecting these areas in PD was responsible for impaired performance on mental rotation tasks. There are, however, several reasons to be cautious about putting too much stock in this interpretation of the results of Experiment 4. First, the abnormal processing observed in SMA and M1 in the studies discussed above was relatively normalized through treatment with levodopa (Wu et al., 2009; Haslinger et al., 2001), and the motor symptoms related to these processing irregularities were improved with dopaminergic medications (Ng et al., 2017; Jenkins et al., 1992). In contrast, the impairments seen in individuals with PD for mental rotation in Experiment 4 were refractory to levodopa treatment. Thus, if impaired functioning in these motor areas contributed to poor performance by the PD group, then at minimum the neural mechanisms through which this occurred must be different from those that produce motor symptoms. Second, if the reader is not persuaded that the group difference observed for the mental rotation task represents a meaningful increase over those of the previous four tasks, then strong conclusions based on this interpretation will obviously be unpersuasive. Further research, ideally including imaging studies, should be conducted to establish the differences in neural activity between mental rotation tasks and more simple discrimination tasks. Such research should also further examine what role, if any, DA plays in mental rotation impairments in individuals with PD.

CHAPTER 9: GENERAL DISCUSSION

9.1 Summary

The purpose of this study was to examine the effects of DA and dopaminergic medications on ventral pathway-dependent visual processing in individuals with PD. A variety of visual deficits have been reported to accompany PD (see section 1.5), and since the symptomology of PD is largely the result of DA dysregulation, it followed that these visual deficits could also be DA-dependent. The mechanisms of action for levodopa, a DA precursor medication, have the effect of raising global levels of DA using the brain's own mechanisms for DA synthesis, effectively normalizing DA levels in areas of the brain that are DA-deprived so long as the underlying circuitry remains intact. Therefore, observing the performance of individuals with PD on cognitive visual tasks both while they were on and off of their levodopa medication afforded the opportunity to examine the effects of DA under reasonably controlled conditions. Given the nature of PD pathology, and citing previous literature reporting that treatment with dopaminergic medications had improved symptoms in lower visual processing, the author predicted that participants in the PD group would be impaired relative to their healthy counterparts across all experimental tasks, and that administration of levodopa would improve performance to levels near or equal to the HOA group. The tasks included in this study were selected for their ability to recruit different constellations of cortical processing resources so that any differential response to DA manipulation might provide an indication of which brain regions were responsible for performance impairments. As anticipated, the PD group performed significantly worse than the HOA group across all tasks, providing support for the thesis that ventral pathway-dependent visual processing is typically impaired in cases of PD. However, performance deficits in the PD group were unaffected by the administration of levodopa, suggesting that mechanisms other than DA depletion were responsible for impairments in cognitive vision. Further, given that there were no dramatic changes in mean difference between groups across tasks (save, perhaps, the final task), the implications for what specific brain

regions or impaired visual processes might be responsible for cognitive visual deficits require a somewhat nuanced interpretation.

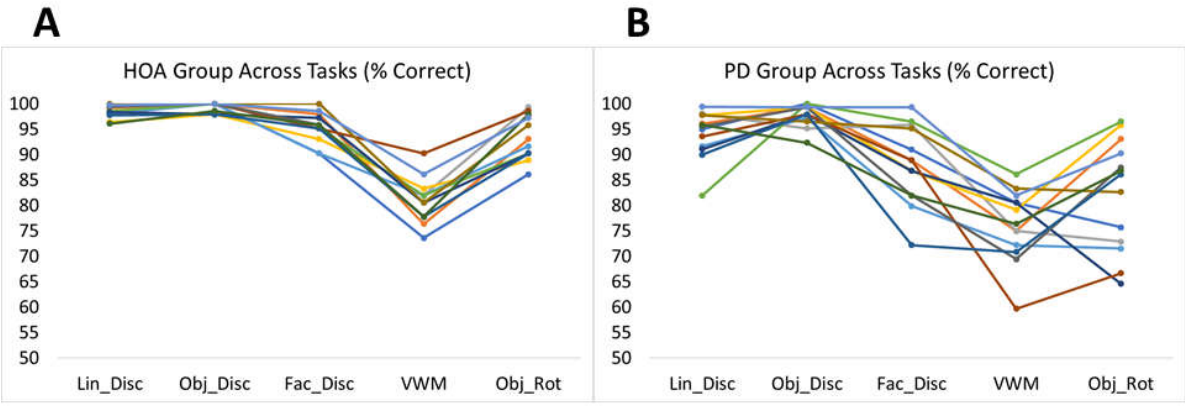


Figure 27. Participant performance across experimental tasks, collapsed across session. A: Healthy Older Adult group. B: Parkinson's Disease group. 50% represented chance performance on all tasks.

9.2 Aim 1:

Aim 1 of the current study was to examine any effect of DA and dopaminergic medications on ventral pathway-dependent visual processing. If the visual deficits observed in the various experimental tasks had been a result of DA depletion or overdose in individuals with PD, this would have been indicated by an interaction between session and group. In the simplest case, performance for the PD group would have been altered between sessions as a result of levodopa administration, while no analogous change would have been observed in the HOA group. Alternatively, performance by the HOA group could have been changed by some additional factor, such as fatigue or practice, while a change in performance by the PD group would have differed in degree or in kind. Only the results of Experiment 2a exhibited this pattern, where the PD group performed worse at abstract object discrimination in the afternoon than in the morning, while performance by the HOA group exhibited no significant change between sessions.

Such a finding is consistent with the Dopamine Overdose Hypothesis, which states that dopaminergic circuitry that is relatively unaffected in the early stages of PD is adversely affected by the

administration of dopaminergic medications because an excess of DA prevents the circuitry from functioning properly (Poletti & Bonuccelli, 2013; Graef et al., 2010) (see section 1.6.3). It is at least plausible that there is some brain area or process uniquely recruited in the object discrimination task that is particularly susceptible to impairment via excess DA, and further research should be conducted to examine this possibility. However, given that the three subsequent experimental tasks also require some level of discrimination of similarly complex visual stimuli, it seems doubtful that the object discrimination task would evince a response to levodopa administration while later tasks would not. One thing that stands out about the results of Experiment 2a is that both groups scored at or near ceiling on the object discrimination task. Given that cognitive load was likely not a factor driving group differences, it is likely that poorer performance by the PD group in the afternoon was caused by boredom or fatigue later in the study protocol. This interpretation is bolstered by an effect of session observed in Experiment 1, where participants from both groups again scored at or near ceiling and both groups performed significantly worse during the afternoon session. The much larger number of trials in Experiment 1 (180 compared to 72 in Experiment 2a) may explain why the performance of the HOA group also suffered in the afternoon for the line discrimination task.

While the finding that poor performance by individuals with PD on ventral pathway-dependent visual tasks is unaffected by DA modulation was not predicted, it is not entirely surprising. A number of studies have found that cognitive symptoms are less responsive to DA manipulation than motor symptoms. A study by Lange et al. (1992) tested individuals with PD both while on their dopaminergic medications and following withdrawal for tasks involving attention, memory, learning, and planning. These researchers found that DA modulation had no significant effect on performance of spatial or pattern recognition memory tasks, simultaneous or delayed match-to-sample tasks, or visual associative learning tasks. Indeed, the only cognitive tasks in which accuracy was affected by levodopa withdrawal were learning and memory tasks known to be strong indicators of frontal lobe function. Of particular

relevance to the current study, Pillon and colleagues (1989) also examined the effects of levodopa in cognitive vision in individuals with PD. The experimenters administered a task in which participants were instructed to identify common objects depicted in 15 line drawings superimposed on one another and found no difference in performance when individuals were in ON-meds vs. OFF-meds states. While the 15-object task employed in that study also involved ventral pathway-dependent visual processing of objects, it differed from the present study in that it involved the retrieval of semantic information about target objects, a process previously shown to aid visual processing of object stimuli (Grossman, Galetta, & D'Esposito, 1997), possibly by recruiting additional processing resources in the perirhinal cortex (Lehky & Tanakam 2016). However, to the best of the author's knowledge, the observation that impaired visual discrimination and spatial transformation of novel objects observed in individuals with PD is also refractory to DA therapy is a novel finding of the present study.

9.3 Aim 2:

Aim 2 of the present study was to examine the neural basis of visual impairments observed in individuals with PD. In the introduction the author outlined three methods by which abnormal DA signaling could produce impairments in cognitive vision. They were as follows:

- Model 1: Previously characterized PD pathology in the BG may lead to performance deficits for visual tasks that recruit processing resources from the striatum.
- Model 2: PD may lead to impaired dopaminergic signaling in areas of the visual system itself that are required for performance of visual tasks.
- Model 3: Dopaminergic activity within the visual system or other critical areas that is relatively spared in the early stages of PD may be disrupted by the dopaminergic medication used to treat the disease.

An additional model was also proposed in which impairments to cognitive vision resulted from mechanisms that were not dopaminergic in nature:

- Model 4: Visual symptoms may be related to more general brain pathology.

If Model 1 or 3 had been correct, we would have predicted some effect of levodopa on task performance by the PD group in this study. The basis for Model 1 was the reciprocal connectivity between the BG and the ventral visual pathway (Kravitz et al., 2013; Seger et al., 2013), as well as lesion studies showing that damage to the BG could disrupt visual discrimination in macaques (Divac et al., 1967). Model 3 was inspired by the Dopamine Overdose Hypothesis, which was proposed to explain why dopaminergic medication had been observed to improve performance on some cognitive tasks for individuals with PD while impairing performance on other tasks (Poletti & Bonuccelli, 3013). In either case, transitioning from an OFF-meds state to an ON-meds state should have yielded some measurable difference in task performance, but this was not observed for this study in a manner that could not be better explained by other situational factors.

Whether or not the pattern of the results reported here is consistent with Model 2 requires a better understanding of the role that DA plays in visual areas than exists in the present literature, as well as research into how dopaminergic circuitry in these areas is affected by PD. Model 2 was based on the observation that DA receptors are ubiquitous throughout the human visual system at varying levels of expression (Hurd, Suzuki, & Sedvall, 2001; Djamgoz & Wagner, 1992). As such, pathology of these receptors or deficiency in the levels of DA that they bind could affect visual processing in unpredictable ways. Therefore, the diminished task performance observed for the PD group across sessions in this study would still be consistent with Model 2 if the dopaminergic circuitry had degraded past the point where levodopa could have a therapeutic effect (e.g., if L-DOPA could not be successfully converted to DA, or if too few receptors remained intact).

In contrast, an effect of group that does not respond to modulation of DA levels is the prediction that follows naturally from Model 4. As noted previously, PD is associated with a number of biomarkers in addition to DA depletion in the BG. For instance, studies have shown that PD is associated with

microstructural changes in both grey and white matter that appear to scale with disease severity (Surova et al., 2016), while PD sufficient to produce mild cognitive impairment has been associated with hypometabolism and atrophy of both grey and white matter in broadly distributed areas of the brain (Gonzalez-Redondo et al., 2014; Agosta et al., 2013). In the case of the visual processing of faces in particular, task impairments have been shown to correlate with grey matter loss in an area critical to face recognition (Periera et al., 2009). Additionally, researchers have recently reported retinal pathology in PD that includes phosphorylated and misfolded α-synuclein (Beach et al., 2014; Bodis-Wollner et al., 2014). There are thus a variety of candidate mechanisms that could be responsible for observed impairments in cognitive vision absent any role of dopaminergic circuitry *per se*. While the results of this study likely rule out several DA-based accounts of how cognitive visual impairments arise in individuals with PD, a conclusive account of the mechanisms that are responsible will require further research.

This study was also designed to employ tasks that could provide evidence concerning which areas the visual system might be the source of any observed visual impairment. Specifically, each of the five visual tasks in the current study have been found in previous studies to recruit a slightly different constellation of visual areas. If PD pathology had disproportionately affected any of these areas, we would have predicted that some appreciable number of individuals in the PD group would have performed at or near chance for tasks that required processing in this area while all members of the HOA group remained comparatively unaffected. For example, if the PFC deteriorated significantly in PD while the ventral visual pathway itself was largely spared, we would predict that members of the PD group would perform at or near chance on the VWM and mental rotation tasks while showing little or no deficit on the first three tasks. On the other hand, if PD pathology was specific to early visual areas such as the retina or V1, we would expect members of the PD group to perform close to chance on all five tasks.

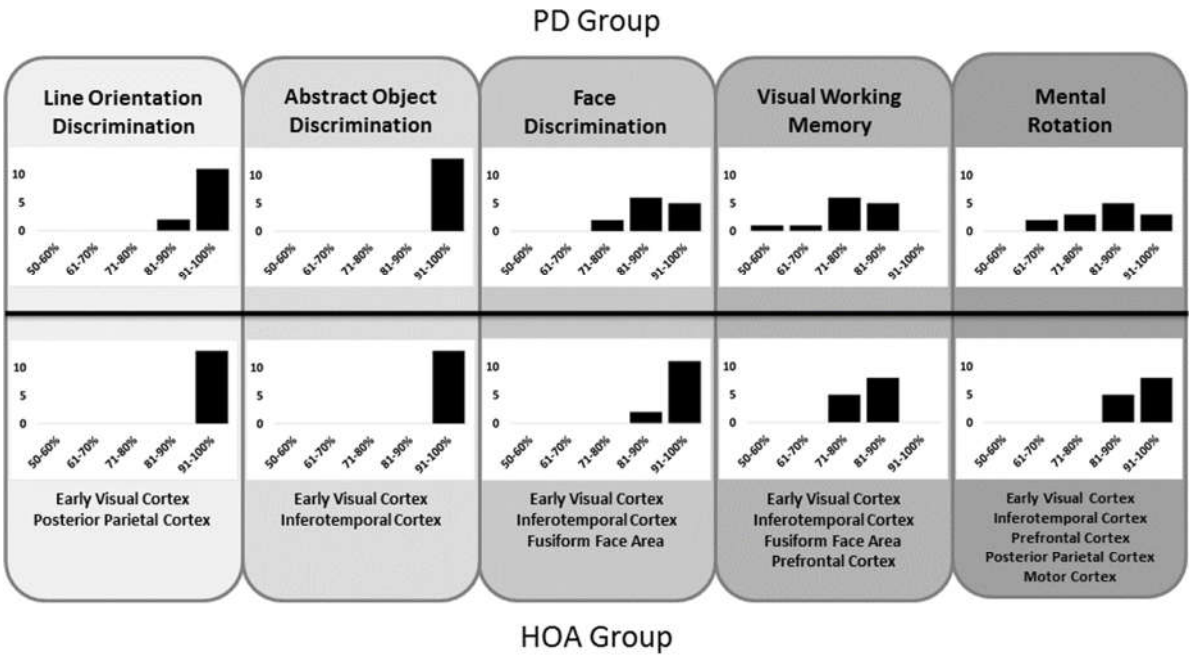


Figure 28. Distribution of participant scores across tasks. Tasks are broken down according to brain regions thought to be critical for performance of each. The x-axis of each graph is task score, ranging from 50% (chance) to 100% (perfect), while the y-axis represents the number of scores observed within the indicated range.

However, no dramatic drop to chance level was observed for the PD group for any task. Instead, the PD group performed significantly worse than the HOA group on all tasks while never showing a profound deficit on any one. It is notable that one individual in the PD group scored less than 60% on the VWM task. However, this is perhaps not surprising given that both groups performed appreciably worse on this task, meaning that an individual in the PD group performing close to chance might be predicted based simply on task difficulty. In support of this interpretation, it is notable the mean score of the PD group was closer to the HOA group in the VWM task (4.46% mean difference) than in the face discrimination task (7% mean difference). In other words, the PD group overall scored closer to chance for VWM task, but actually performed closer to baseline than on the previous, easier task.

One way to account for the pattern of results observed in this study would be to postulate that two regions critical for these tasks were particularly susceptible to PD pathology: one in the early visual system and one in motor cortical regions. The former would account for the small but persistent group

differences observed in the first four tasks. It may simply be that whatever damage produced the impaired fine visual discrimination observed in the line discrimination task produced a similar impairment in the discrimination of the object and face stimuli used in this study. In this view, studies that have previously reported PD-related impairments in tasks like the FRT may simply have observed a generalized discrimination deficit as opposed to one specific to faces. Exactly what impaired process might produce this deficit is not clear. Group differences in acuity should theoretically have been negligible since both groups were required to have normal or corrected-to-normal vision as judged by a relatively recent eye exam (no more than a year prior). Group differences in contrast sensitivity also cannot completely account for group differences in task performance because stimuli in the line discrimination task were at maximal contrast with their background, though the same was not true for the later face and object stimuli. One possibility is that orientation selectivity itself is the root of the deficit observed in individuals with PD, resulting from damage anywhere between the retina and early cortical visual areas. This is obviously speculation, since the observed pattern of results may be consistent with a number of other deficits as well. If this or a similar study were conducted in the future, researchers should consider performing an acuity test of all participants during the data collection to rule acuity out as a source of impairment for individuals with PD. The design of the current study leaves open the possibility that individuals from either group may have misremembered the date of their most recent eye appointment, or that their vision may have deteriorated precipitously during the time since their checkup. It may also be prudent in the future to add a manipulation that examines the effect of varying contrasts, perhaps by including only black-and-white stimuli instead of grey scale, as well as a manipulation that examines the effect of spatial frequency, likely through the manipulation of stimulus images using software packages with spatial frequency filtering.

On the other hand, impairment of the motor cortical regions would account for the increase in effect of group observed in Experiment 4. While previous research has indicated that individuals with PD

may be impaired relative to their healthy counterparts for mental rotation tasks (see Lee et al., 1998), the results of Experiment 4 in this study raise the possibility that the source of this impairment may be diminished processing in motor regions of the brain. This position is supported by research suggesting a role for motor cortical areas in mental simulation and emulation (Cona & Semenza, 2017; Ptak et al., 2017) and research indicating that these areas show altered or diminished function in PD (Wu et al., 2009; Haslinger et al., 2001; Rascol et al., 1994). Researchers wishing to follow up on the present study would benefit greatly from neural imaging, and fMRI in particular, to compare activity in M1, SMA, and lateral premotor cortices between individuals with PD and their healthy counterparts. This would ideally be done while continuing to observe individuals with PD in both ON- and OFF-meds states to determine if activity in brain areas recruited for all tasks is affected in ways that may not influence task performance (e.g., if DA activity is being normalized in the ON-meds states by some compensatory mechanisms).

9.4 Implications for Individuals with PD

Because the results of the current study indicated no changes in ventral pathway-dependent vision for individuals with PD between ON- and OFF-meds states, there appears to be no basis for concern that administration of levodopa will lead to difficulties in everyday visual processing. There also appears to be no basis for concluding that such medication could provide a therapeutic benefit for existing cognitive visual impairments. While further research should be conducted to confirm these findings, modulation of DA in the brain appears to have no effect on cognitive vision sufficient to impact an individual's activities of daily living.

Likewise, performance impairments observed in the PD group in this study are likely insufficient to disrupt the daily activities of individuals with PD. While differences between the PD group and their healthy counterparts were statistically significant for all experimental tasks, effect sizes were relatively small, and the stimuli used were constrained in their design for the purposes of laboratory testing. So,

for instance, poorer performance by individuals with PD on the face discrimination task would not likely translate into difficulty learning and remembering novel faces in the real world, where numerous other cues to identity are available. Similarly, trials in the VWM task have no obvious analog in everyday activities, since individuals are seldom required to make detailed discriminations of complex objects following extremely minimal exposure times. Future studies should nevertheless be conducted to investigate the ability of individuals with PD to discriminate stimuli under more ecologically valid conditions.

9.5 Conclusion

This study was designed to investigate the effects of DA and dopaminergic medications on impairments to high-level vision in PD. Despite the key role that DA depletion plays in much of the pathology of PD, the results of the present study provide strong evidence that modulation of DA levels does not improve or impair cognitive vision in individuals with PD. The absence of an effect of levodopa in the performance of object and face discrimination tasks, visual working memory tasks, and mental rotation tasks represents a novel finding in visual research. Additionally, the finding that impairments to complex object discrimination do not appreciably exceed similar impairments in line orientation discrimination raises the possibility that high-level visual impairments reported here and elsewhere are actually the result of low-level visual impairments, and supports the use of appropriate control tasks when examining cognitive vision in PD. Finally, the results of this study provide cursory evidence that mental rotation deficits in PD may the result of impaired processing in motor areas of the brain, though more research is needed on this topic.

REFERENCES

1. Agosta, F., Canu, E., Stefanova, E., Sarro, L., Tomić, A., Špica, V., Comi, G., Kostić, V.S., & Filippi, M. (2014). Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. *Human Brain Mapping, 35*(5), 1921-1929. doi: 10.1002/hbm.22302

2. Amick, M.M., Schendan, H.E., Ganis, G., & Cronin-Golomb, A. (2006). Frontostriatal circuits are necessary for visuomotor transformation: Mental rotation in Parkinson's disease. *Neuropsychologia, 44*(3), 339-349. doi: 10.1016/j.neuropsychologia.2005.06.002

3. Ball, S.G., & Lee, M.R. (1977). The effect of carbidopa administration on urinary sodium excretion in man: Is dopamine an intrarenal natriuretic hormone? *British Journal of Clinical Pharmacology, 4*(2), 115-119. doi: 10.1111/j.1365-2125.1977.tb00681.x

4. Bengtsson, S.L., Csikszentmihalyi, M., & Ullén, F. (2007). Cortical regions involved in the generation of musical structures during improvisation in pianists. *Journal of Cognitive Neuroscience, 19*(5), 830-842. doi: 10.1162/jocn.2007.19.5.830

5. Benton, A.L., Varney, N.R., & Hamsher, K.D. (1978). Visuospatial judgment: A clinical test. *Archives of Neurology, 35*(6), 364-367. doi: 10.1001/archneur.1978.00500300038006

6. Beach, T.G., Carew, J., Serrano, G., Adler, C.H., Shill, H.A., Sue, L.I., Sabbagh, M.N., Akiyama, H., Cuenca, N., & Arizona Parkinson's Disease Consortium (2014). Phosphorylated α-synuclein-immunoreactive retinal neuronal elements in Parkinson's disease subjects. *Neuroscience Letters, 571*, 34-38. doi: 10.1016/j.neulet.2014.04.027

7. Biousse, V., Skibell, B.C., Watts, R.L., Loupe, D.N., Drews-Botsch, C., & Newman, N.J. (2004). Ophthalmologic features of Parkinson's disease. *Neurology, 62*(2), 177-180. doi: 10.1212/01.WNL.0000103444.45882.D8

8. Bodis-Wollner, I. (1990). Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. *Trends in Neurosciences, 13*(7), 296-302. doi: 10.1016/0166-2236(90)90113-O

9. Bodis-Wollner, I., & Yahr, M.D. (1978). Measurements of visual evoked potentials in Parkinson's disease. *Brain, 101*(4), 661-671. doi: 10.1093/brain/101.4.661

10. Bowers, D., Blonder, L.X., & Heilman, K.M. (1991). *The Florida Affect Battery*. Center for Neuropsychological Studies – University of Florida

11. Brichta, L., Greengard, P., & Flajolet, M. (2013). Advances in the pharmacological treatment of Parkinson's disease: Targeting neurotransmitter systems. *Trends in Neurosciences, 36*(9), 543-554. doi: 10.1016/j.tins.2013.06.003

12. Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., & Di Lizzaro, V. (2001). Dopamine dependency of oscillation between subthalamic nucleus and pallidum in Parkinson's disease. *The Journal of Neuroscience, 21*(3), 1033-1038. doi: 10.1523/JNEUROSCI.21-03-01033.2001

13. Burton, E.J., McKeith, I.G., Burn, D.J., Williams, E.D., & O'Brien, J.T. (2004). Cerebral atrophy in Parkinson's disease with and without dementia: A comparison with Alzheimer's disease, dementia with Lewy bodies, and controls. *Brain, 127*(4), 791-800. doi: 10.1093/brain/awh088

14. Büttner, T., Kuhn, W., Patzold, T., & Przuntek, H. (1994). L-DOPA improves color vision in Parkinson's disease. *Journal of Neural Transmission – Parkinson's Disease and Dementia Section, 7*(1), 13-19. doi: 10.1007/BF02252659

15. Callaway, E.M. (2005). Structure and function of parallel pathways in the primate early visual system. *The Journal of Physiology, 566*(1), 13-19. doi: 10.1113/jphysiol.2005.088047

16. Campbell, F.W., & Maffei, L. (1974). Contrast and Spatial Frequency. *Scientific American, 231*(5), 106-115. doi: 10.1038/scientificamerican1174-106

17. Campo, P., & Morales, M. (2003). Reliability and normative data for the Benton visual form discrimination test. *The Clinical Neuropsychologist, 17*(2), 220-225. doi: 10.1076/clin.17.2.220.16504

18. Christophel, T.B., Cichy, R.M., Hebart, M.N., & Haynes, J.-D. (2015). Parietal and early visual cortices encode working memory content across mental transformations. *NeuroImage, 106*, 198-206. doi: 10.1016/j.neuroimage.2014.11.018

19. Cisek, P., & Kalaska, J.F. (2005). Neural correlates of reaching decisions in dorsal premotor cortex: Specification of multiple direction choices and final selection of action. *Neuron, 45*(5), 801-814. doi: 10.1016/j.neuron.2005.01.027

20. Cohen, M.S., Kosslyn, S.M., Breiter, H.C., DiGirolamo, G.J., Thompson, W.L., Anderson, A.K., Bookheimer, S.Y., Rosen, B.R., & Belliveau, J.W. (1996). Changes in cortical activity during mental rotation: A mapping study using functional MRI. *Brain, 119*(1), 89-100. doi: 10.1093/brain/119.1.89

21. Cona, G., & Semenza, C. (2017). Supplementary motor area as key structure for domain-general sequence processing: A unified account. *Neuroscience and Biobehavioral Reviews, 72*, 28-42. doi: 10.1016/j.neubiorev.2016.10.033

22. Cona, G., Marino, G., & Semenza, C. (2017a). The role of dorsal premotor cortex in mental rotation: A transcranial magnetic stimulation study. *Brain and Cognition, 116*, 71-78. doi: 10.1016/j.bandc.2017.06.002

23. Cona, G., Marino, G., & Semenza, C. (2017b). TMS of supplementary motor area (SMA) facilitates mental rotation performance: Evidence for sequence processing in SMA. *Neuroimage, 146*, 770-777. doi: 10.1016/j.neuroimage.2016.10.032

24. Cools, R. (2006). Dopaminergic modulation of cognitive function: Implications for L-DOPA treatment in Parkinson's disease. Neuroscience & Biobehavioral Reviews, 30(1), 1-23. doi: 10.1016/j.neubiorev.2005.03.024

25. Cools, R., Barker, R.A., Sahakian, B.J., & Robbins, T.W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia, 41, 1431-1441. doi: 10.1016/S0028-3932(03)00117-9

26. Cooper, E.E., & Wojan, T.J. (2000). Differences in the coding of spatial relations in face identification and basic-level object recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26*(2), 470-488. doi: 10.1037/0278-7393.26.2.470

27. Courtney, S.M., Ungerleider, L.G., Keil, K., & Haxby, J.V. (1996). Object and spatial working memory activate separate neural systems in human cortex. *Cerebral Cortex, 6*(1), 39-49. doi: 10.1093/cercor/6.1.39

28. Courtney, S.M., Ungerleider, L.G., Keil, K., & Haxby, J.V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature, 386*(6625), 608-611. doi: 10.1038/386608a0

29. Crowe, D.A., Zarco, W., Bartolo, R., & Merchant, H. (2014). Dynamic representation of the temporal and sequential structure of rhythmic movements in the primate medial premotor cortex. *The Journal of Neuroscience, 34*(36), 11972-11983. doi: 10.1523/JNEUROSCI.2177-14.2014

30. Cudeiro, J., & Sillito, A.M. (2006). Looking back: Corticothalamic feedback and early visual processing. *Trends in Neurosciences, 29*(6), 298-306. doi: 10.1016/j.tins.2006.05.002

31. Demb, J.B., & Singer, J.H. (2015). Functional circuitry of the retina. *Annual Review of Visual Science, 1*, 263-289. doi: 10.1146/annurev-vision-082114-035334

32. Divac, I., Rosvold, H.E., & Szwarcbart, M.K. (1967). Behavioral effects of selective ablation of the caudate nucleus. *Journal of Comparative and Physiological Psychology, 63*(2), 184-190. doi: 10.1037/h0024348

33. Djamgoz, M.B.A., & Wagner, H.-J. (1992). Localization and function of dopamine in the adult vertebrate retina. *Neurochemistry International, 20*(2), 139-191. doi: 10.1016/0197-0186(92)90166-O

34. Double, K.L., Halliday, G.M., McRitchie, D.A., Reid, W.G.J., Hely, M.A., & Morris, J.G.L. (1996). Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. *Dementia and Geriatric Cognitive Disorders, 7*(6), 304-313. doi: 10.1159/000106896

35. Duchaine, B.C., & Weidenfeld, A. (2003). An evaluation of two commonly used tests of unfamiliar face recognition. *Neuropsychologia, 41*(6), 713-720. doi: 10.1016/S0028-3932(02)00222-1

36. Elsworth, J.D., & Roth, R.H. (1997). Dopamine synthesis, uptake, metabolism, and receptors: Relevance to gene therapy of Parkinson's disease. *Experimental Neurology, 144*(1), 4-9. doi: 10.1006/exnr.1996.6379

37. Farah, M.J., Levinson, K.L., & Klein, K. (1995). Face perception and within-category discrimination in prosopagnosia. *Neuropsychologia, 33*(6), 661-674. doi: 10.1016/0028-3932(95)00002-K

38. Farah, M.J., Wilson, K.D., Drain, H.M., & Tanaka, J.W. (1995). The inverted face inversion effect in prosopagnosia: Evidence for mandatory, face-specific perceptual mechanisms. *Vision Research, 35*(14), 2089-2093. doi: 10.1016/0042-6989(94)00273-O

39. Finton, M.J., Lucas, J.A., Graff-Radford, N.R., & Uitti, R.J. (1998). Analysis of visuospatial errors in patients with Alzheimer's disease and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 20*(2), 186-193. doi: 10.1076/jcen.20.2.186.1167

40. Flowers, K.A., & Robertson, C. (1995). Perceptual abnormalities in Parkinson's disease: top-down or bottom-up processes? *Perception, 24*, 1201-1221. doi: 10.1068/p241201

41. Friedman, J.H., Brown, R.G., Comella, C., Garber, C.E., Krupp, L.B., Lou, J.-S., Marsh, L., Nail, L., Shulman, L., & Taylor, C.B. (2006). Fatigue in Parkinson's disease: A review. *Movement Disorders, 22*(3), 297-308. doi: 10.1002/mds.21240

42. Ganis, G., Keenan, J.P., Kosslyn, S.M., & Pascual-Leone, A. (2000). Transcranial magnetic stimulation of primary motor cortex affects mental rotation. *Cerebral Cortex, 10*(2), 175-180. doi: 10.1093/cercor/10.2.175

43. Ganis, G. & Kievit, R.A. (2015). A New Set of Three-Dimensional Shapes for Investigating Mental Rotation Processes: Validation Data and Stimulus Set. *Journal of Open Psychology Data*, *3*(1). doi: 10.5334/jopd.ai

44. Gauthier, I., Anderson, A.W., Tarr, M.J., Skudlarski, P., & Gore, J.C. (1997). Levels of categorization in visual recognition studied using functional magnetic resonance imaging. *Current Biology, 7*(9), 645-651. doi: 10.1016/S0960-9822(06)00291-0

45. Gayet, S., Paffen, C.L.E., & Van der Stigchel, S. (2018). Visual working memory storage recruited sensory processing areas. *Trends in Cognitive Sciences, 22*(3), 189-190. doi: 10.1016/j.tics.2017.09.011

46. Gaymard, B., Pierrot-Deseilligny, C., & Rivand, S. (1990). Impairment of sequences of memory-guided saccades after supplementary motor area lesions. *Annals of Neurology, 28*(5), 622-626. doi: 10.1002/ana.410280504

47. Gerfen, C.R., & Surmeier, D.J. (2011). Modulation of striatal projection systems by dopamine. *Annual Review of Neuroscience, 34*, 441-166. doi: 10.1146/annurev-neuro-061010-113641

48. Gilbert, C.D., & Li, W. (2013). Top-down influences on visual processing. *Nature Reviews Neuroscience, 14*(5), 350-363. doi: 10.1038/nrn3476

49. Graef, S., Biele, G., Krugel, L.K., Marzinzik, F., Wahl, M., Wotka, J., Klostermann, F., & Heekeren, H.R. (2010). Differential influence of levodopa on reward-based learning in Parkionson's disease. Frontiers in Human Neuroscience, 4, 1-13. doi: 10.3389/fnhum.2010.00169

50. González-Redondo, R., García-García, D., Clavero, P., Gasca-Salas, C., García-Eulate, R., Zubieta, J.L., Arbizu, J., Obeso, J.A., & Rodríguez-Oroz, M.C. (2014). Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. *Brain, 137*(8), 2356-2367. doi: 10.1093/brain/awu159

51. Grèzes, J., & Decety, J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: A meta-analysis. *Human Brain Mapping, 12*(1), 1-19. doi: 10.1002/1097-0193(200101)12:13.0.CO;2-V

52. Grossman, M., Galetta. S., & D'Esposito, M. (1997). Object recognition difficulty in apperceptive agnosia. *Brain and Cognition, 33*(3), 306-342. doi: 10.1006/brcg.1997.0876

53. Gurevich, E.V., & Gurevich, V.V. (2010). Dopamine receptors and the treatment of Parkinson's disease. in Neve, K.A. (Eds.), *The Dopamine Receptors* (pp. 525-584). New York, NY: Humana Press.

54. Haslinger, B., Erhard, P., Kämpfe, N., Boecker, H., Rummeny, E., Schwaiger, M., Conrad, B., & Ceballos-Baumann, A.O., (2001). Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain, 124*(3), 558-570. doi: 10.1093/brain/124.3.558

55. Haxby, J.V., Grady, C.L., Horwitz, B., Ungerleider, L.G., Mishkin, M., Carson, R.E., Herscovitch, P., Schapiro, M.B., & Rapoport, S.I. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proceedings of the National Academy of Sciences, 88*(5), 1621-1625. doi: https://doi.org/10.1073/pnas.88.5.1621

56. Hubel, D.H., & Wiesel, T.N. (1959). Receptive fields of single neurones in the cat's striate cortex. *Journal of Physiology, 148*(3), 574-591. doi: 10.1113/jphysiol.1959.sp006308

57. Hubel, D.H., & Wiesel, T.N. (1968). Receptive fields and functional architecture of monkey striate cortex. *Journal of Physiology, 195*(1), 215-243. doi: 10.1113/jphysiol.1968.sp008455

58. Hurd, Y.L., Suzuki, M., & Sedvall, G.C. (2001). D1 and D2 dopamine receptor mRNA expression in whole hemisphere sections of the human brain. *Journal of Chemical Neuroanatomy, 22*(1-2), 127-137. doi: 10.1016/S0891-0618(01)00122-3

59. Jacobs, D.H., Shuren, J., Bowers, D., & Heilman, K.M. (1995). Emotional facial imagery, perception, and expression in Parkinson's disease. *Neurology, 45*(9), 1696-1702. doi: 10.1212/WNL.45.9.1696

60. Janssen, P., Verhoef, B.-M., & Premereur, E. (2018). Functional interactions between the macaque dorsal and ventral visual pathways during three-dimensional object vision. *Cortex, 98*, 218-227. doi: 10.1016/j.cortex.2017.01.021

61. Jefferson, A.L., Powers, D.V., & Pope, M. (2008). Beck Depression Inventory-II (BDI-II) and Geriatric Depression Scale (GDS) in older women. *Clinical Gerontologist, 22*(3-4), 3-12. doi: 10.1300/J018v22n03_02

62. Jenkins, I.H., Fernandez, W., Playford, E.D., Lees, A.J., Frackowiak, R.S.J., Passingham, R.E., & Brooks, D.J. (1992). Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. *Annals of Neurology, 32*(6), 749-757. doi: 10.1002/ana.410320608

63. Jones, R.D., Donaldson, I.M., & Timmings, P.L. (1992). Impairment of high-contrast visual acuity in Parkinson's disease. *Movement Disorders, 7*(3), 232-238. doi: 10.1002/mds.870070308

64. Jordan, K., Heinze, H.-J., Lutz, K., Kanowski, M., & Jäncke, L. (2001). Cortical activations during the mental rotation of different visual objects. *NeuroImage, 13*(1), 143-152. doi: 10.1006/nimg.2000.0677

65. Junqué, C., Alegret, M., Nobbe, F.A., Valldeoriola, F., Pueyo, R., Vendrell, P., Tolosa, E., Rumià, J., & Mercader, J.P. (1999). Cognitive and behavioral changes after unilateral posteroventral pallidotomy: Relationship with lesion data from MRI. *Movement Disorders, 14*(5), 780-789. doi: 10.1002/1531-8257(199909)14:5<780::AID-MDS1010>3.0.CO;2-G

66. Kanwisher, N., McDermott, J., & Chun, M.M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience, 17*(11), 4302-4311. doi: 10.1523/JNEUROSCI.17-11-04302.1997

67. Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M.M., Turner, R., & Ungerleider, L.G. (1998). The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences USA, 95*(3), 861-868. doi: 10.1073/pnas.95.3.861

68. Katsuyama, N., Yamashita, A., Sawada, K., Naganuma, T., Sakata, H., & Taira, M. (2010). Functional and histological properties of caudal intraparietal areas of the macaque monkey. *Neuroscience, 167*(1), 1-10. doi: 10.1016/j.neuroscience.2010.01.028

69. Kim, S.-H., Park, J.-H., Kim, Y.H., & Koh, S.-B. (2011). Stereopsis in drug naïve Parkinson's disease patients. *The Canadian Journal of Neurological Sciences, 38*(2), 299-302. doi: 10.1017/S0317167100011501

70. Koh, S.-B., Suh, S., Kim, S.-H., & Kim, J.H. (2013). Stereopsis and extrastriate cortical atrophy in Parkinson's disease: A voxel-based morphometric study. *NeuroReport, 24*(5), 229-232. doi: 10.1097/WNR.0b013e32835edbc5

71. Kravitz, D.J., Saleem, K.S., Baker, C.I., Ungerleider, L.G., & Mishkin, M. (2013). The ventral visual pathway: An explanded neural framework for the processing of object quality. *Trends in Cognitive Science, 17*(1), 26-49. doi: 10.1016/j.tics.2012.10.011

72. Laatu, S., Revonsuo, A., Pihko, L., Portin, R., & Rinne, J.O. (2004). Visual object recognition deficits in early Parkinson's disease. *Parkinsonism and Related Disorders, 10*(4), 227-233. doi: 10.1016/j.parkreldis.2004.02.001

73. Lange, K.W., Robbins, T.W., Marsden, C.D., James, M., Owen, A.M., & Paul, G.M. (1992). L-DOPA withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology, 107*(2-3), 394-404. doi: 10.1007/BF02245167

74. Laudate, T.M., Neargarder, S., & Cronin-Golomb, A. (2013). Line bisection in Parkinson's disease: Investigation of contributions of visual field, retinal vision, and scanning patterns in visuospatial function. *Behavioral Neuroscience, 127*(2), 151-163. doi: 10.1037/a0031618

75. Lee, A.C., Harris, J.P., & Calvert, J.E. (1998). Impairments of mental rotation in Parkinson's disease. *Neuropsychologia, 36*(1), 109-114. doi: 10.1016/S0028-3932(97)00017-1

76. Lehky, S.R., & Tanaka, K. (2016). Neural representation for object recognition in the inferotemporal cortex. *Current Opinion in Neurobiology, 37*, 23-35. doi: 10.1016/j.conb.2015.12.001

77. Levin, B.E., Llabre, M.M., Reisman, S., Weiner, W.J., Sanchez-Ramos, J., Singer, C., & Brown, M.C. (1991). Visuospatial impairment in Parkinson's disease. *Neurology, 41*(3), 365-369. doi: 10.1212/WNL.41.3.365

78. Liu, X., Hairston, J., Schrier, M., & Fan, J. (2011). Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional imaging studies. *Neuroscience and Biobehavioral Reviews, 35*(5), 1219-1236. doi: 10.1016/j.neubiorev.2010.12.012

79. Logothetis, N.K., Pauls, J., & Poggio, T. (1995). Shape representation in the inferior temporal cortex of monkeys. *Current Biology, 5*(5), 522-563. doi: 10.1016/S0960-9822(95)00108-4

80. McCarthy, G., Puce, A., Gore, J.C., & Allison, T. (1997). Face-specific processing in the human fusiform gyrus. *Journal of Cognitive Neurosciences, 9*(5), 605-610. doi: 10.1162/jocn.1997.9.5.605

81. Melzer, T.R., Watts, W., MacAskill, M.R., Pitcher, T.L., Livingston, L., Keenan, R.J., Dalrymple-Alford, J.C., & Anderson, T.J. (2011). Grey matter atrophy in cognitively impaired Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(2), 188-194. doi: 10.1136/jnnp-2011-300828

82. Menke, R.A.L., Szewczyk-Krolikowski, K., Jbabdi, S., Jenkinson, M., Talbot, K., Mackay, C.E., & Hu, M. (2014). Comprehensive morphometry of subcortical grey matter structures in early-stage Parkinson's disease. *Human Brain Mapping, 35*(4), 1681-1690. doi: 10.1002/hbm.22282

83. Menon, V., Rivera, S.M., White, C.D., Glover, G.H., & Reiss, A.L. (2000). Dissociating prefrontal and parietal cortex activation during arithmetic processing. *Neuroimage, 12*(4), 357-365. doi: 10.1006/nimg.2000.0613

84. Middleton, F.A., & Strick, P.L. (1996). The temporal lobe is a target of output from the basal ganglia. *Proceedings of the National Academy of Sciences, 93*(16), 8683-8687. doi: 10.1073/pnas.93.16.8683

85. Milivojevic, B., Hamm, J.P., & Corballis, M.C. (2009). Functional neuroanatomy of mental rotation. *Journal of Cognitive Neuroscience, 21*(5), 945-959. doi: 10.1162/jocn.2009.21085

86. Miller, E.K., Erickson, C.A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *The Journal of Neuroscience, 16*(16), 5154-5167. doi: 10.1523/JNEUROSCI.16-16-05154.1996

87. Missale, C., Nash, S.R., Robinson, S.W., Jaber, M., & Caron, M.G. (1998). Dopamine receptors: From structure to function. *Physiological Reviews, 78*(1), 189-225. doi: 10.1152/physrev.1998.78.1.189

88. Montse, A., Pere, V., Carme, J., Franscesc, V., & Eduardo, T. (2001). Visuospatial deficits in Parkinson's disease assessed by Judgment of Line Orientation test: Error analysis and practice effects. *Journal of Clinical and Experimental Neuropsychology, 23*(5), 592-598. doi: 10.1076/jcen.23.5.592.1248

89. Muslimović, D., Post, B., Speelman, J.D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson's disease. Neurology, 65(8), 1239-1245. doi: 10.1212/01.wnl.0000180516.69442.95

90. Nath, A., & Schwartz, G.W. (2016). Cardinal orientation selectivity is represented by two distinct ganglion types in mouse retina. *Journal of Neuroscience, 36*(11), 3208-3221. doi: 10.1523/JNEUROSCI.4554-15.2016

91. Ng, B., Varoquaux, G., Poline, J.B., Thirion, B., Greicius, M.D., & Poston, K.L. (2017). Distinct alterations in Parkinson's medication-state and disease-state connectivity. *NeuroImage: Clinical, 16*(C), 575-585. doi: 10.1016/j.nicl.2017.09.004

92. Ogden, J.A., Growdon, J.H., & Corkin, S. (1990). Deficits on visuospatial tests involving forward planning in high-functioning parkinsonians. *Neuropsychiatry, Neuropsychology and Behavioral Neurology, 3*(2), 125-139.

93. Oh, Y.-S., Kim, J.-S., Chung, S.-W., Song, I.-U., Kim, Y.-D., Kim, Y.-I., & Lee, K.-S. (2010). Color vision in Parkinson's disease and essential tremor. *Europena Journal of Neurology, 18*(4), 577-583. doi: 10.1111/j.1468-1331.2010.03206.x

94. Ohara, S., Ikeda, A., Kunieda, T., Yazawa, S., Baba, K., Nagamine, T., Taki, W., Hashimoto, N., Mihara, T., & Shibasaki, H. (2000). Movement-related change electrocortigraphic activity in human supplementary motor area proper. *Brain, 123*(6), 1203-1215. doi: 10.1093/brain/123.6.1203

95. Olin, J.T., Schneider, L.S., Eaton, E.M., Zemansky, M.F., & Pollock, V.E. (1992). The Geriatric Depression Scale and the Beck Depression Inventory as screening instruments in an older adult outpatient population. *Psychological Assessment, 4*(2), 190-192. doi: 10.1037/1040-3590.4.2.190

96. Pereira, J.B., Junqué, C., Martí, M.-J., Ramirez-Ruiz, B., Bargalló, & Tolosa, E. (2009). Neuroanatomical substrate of visuospatial and visuoperceptual impairment in Parkinson's disease. *Movement Disorders, 24*(8), 1193-1199. doi: 10.1002/mds.22560

97. Pillon, B., Dubois, B., Bonnet, A-M, Esteguy, M., Guimaraes, J., Vigouret, J-M., Lhermitte, F., & Agid, Y. (1989). Cognitive slowing in Parkinson's disease fails to respond to levodopa treatment: The 15-object test. *Neurology, 39*(6), 762-768. doi: 10.1212/WNL.39.6.762

98. Poletti, M., & Bonuccelli, U. (2013). Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson's disease: a review. *Therapeutic Advances in Psychopharmacology, 3*(2), 101-113. doi: 10.1177/2045125312470130

99. Potgieser, A.R.E., de Jong, B.M., Wagemakers, M., Hoving, E.W., & Groen, R.J.M. (2014). Insights from supplementary motor area syndrome in balancing movement initiation and inhibition. *Frontiers in Human Neuroscience, 8*(960), 1-11. doi: 10.3389/fnhum.2014.00960

100. Ptak, R., Schnider, A., & Fellrath, J. (2017). The dorsal frontoparietal network: A core system for emulated action. *Trends in Cognitive Sciences, 21*(8), 589-599. doi: 10.1016/j.tics.2017.05.002

101. Rainer, G., Asaad, W.F., & Miller, E.K. (1998). Selective representation of relevant information by neurons in the primate prefrontal cortex. *Nature, 393*, 577-579. doi: 10.1038/31235

102. Rao, S.C., Rainer, G., & Miller, E.K. (1997). Integration of what and where in the primate prefrontal cortex. *Science, 276*(5313), 821-824. doi: 10.1126/science.276.5313.821

103. Rascol, O., Sabatini, U., Chollet, F., Fabre, N., Senard, J.M., Montastruc, J.L., Celsis, P., Marc-Vergnes, J.P., & Rascol, A. (1994). Normal activation in supplementary motor area in patients with Parkinson's disease undergoing long-term treatment with levodopa. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*(5), 567-571. doi: 10.1136/jnnp.57.5.567

104. Regan, D., & Neima, D. (1984). Low contrast letter charts in early diabetic neuropathy, ocular hypertension, glaucoma, and Parkinson's disease. *British Journal of Ophthalmology, 68,* 885-889. doi: 10.1136/bjo.68.12.885

105. Scimeca, J.M., Kiyonaga, A., & D'Esposito, M. (2018). Reaffirming the sensory recruitment account of working memory. *Trends in Cognitive Sciences, 22*(3), 190-192. doi: 10.1016/j.tics.2017.12.007

106. Seger, C.A. (2013). The visual corticostriatal loop through the tail of the caudate: Circuitry and function. *Frontiers in Systems Neuroscience, 7*(104), 1-15. doi: 10.3389/fnsys.2013.00104

107. Shepard, R.N., & Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science, 171*(3972), 701-703. doi: 10.1126/science.171.3972.701

108. Shima, K., & Tanji, J. (2000). Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. *Journal of Neurophysiology, 84*(4), 2148-2160. doi: 10.1152/jn.2000.84.4.2148

109. Ska, B., Poissant, A., & Joanette, Y. (1990). Line orientation judgment in normal elderly and subjects with dementia of Alzheimer's type. *Journal of Clinical and Experimental Neuropsychology, 12*(5), 695-702. doi: 10.1080/12688639008401012

110. Spregelmeyer, R., Young, A.W., Mahn, K., Schroeder, U., Woitalla, D., Buttner, T., Kuhn, W., & Przuntek, H. (2003). Facial expression recognition in people with medicated and unmedicated Parkinson's disease. *Neuropsychologia, 41*(8), 1047-1057. doi: 10.1016/S0028-3932(02)00295-6

111. Stegemöller, E.L., Simuni, T., & MacKinnon, C. (2009). Effect of movement frequency on repetitive finger movements in patients with Parkinson's disease. *Movement Disorders, 24*(8), 1162-1169. doi: 10.1002/mds.22535

112. Sun, L., Zhang, H., Gu, Z., Cao, M., Li, D., & Chan, P. (2014). Stereopsis impairment is associated with decreased color perception and worse motor performance in Parkinson's disease. *European Journal of Medical Research, 19*(29), 1-7. doi: 10.1186/2047-783X-19-29

113. Sunahara, R.K., Dessauer, C.W., & Gilman, A.G. (1996). Complexity and diversity of mammalian adenylyl cyclases. *Annual Review of Pharmacology and Toxicology, 36*, 461-480. doi: 10.1146/annurev.pa.36.040196.002333

114. Surova, Y., Lampinen, B., Nilsson, M., Lätt, J., Hall, S., Widner, H., Swedish BioFINDER Study, van Westen, D., & Hansson, O. (2016). Alterations of diffusion kurtosis and neurite density measures in deep grey matter and white matter in Parkinson's disease. *PLoS ONE, 11*(6), 1-19. doi: 10.1371/journal.pone.0157755

115. Szczypka, M.S., Rainey, M.A., Kim, D.S., Alaynick, W.A., Marck, B.T., Matsumoto, A.M., & Palmiter, R.D. (1999). Feeding behavior in dopamine-deficient mice. *Proceedings of the National Academy of Sciences, 96*(21), 12138-12143

116. Tagaris, G.A., Kim, S.-G., Strupp, J.P., Andersen, P., Uğurbil, K., & Georgopoulos, A.P. (1997). Mental rotation studied by functional magnetic resonance imaging at high field (4 tesla): Performance and cortical activation. *Journal of Cognitive Neuroscience, 9*(4), 419-432. doi: 10.1162/jocn.1997.9.4.419

117. Tanaka, K., Saito, H., Fukada, Y., & Moriya, M. (1991). Coding visual images of objects in the inferotemporal cortex of the macaque monkey. *Journal of Neurophysiology, 66*(1), 170-189. doi: 10.1152/jn.1991.66.1.170

118. Tranel, D., Vianna, E., Manzel, K., Damasio, H., & Grabowski, T. (2009). Neuroanatomical correlates of the Benton Facial Recognition Test and Judgment of Line Orientation Test. *Journal of Clinical and Experimental Neuropsychology, 31*(2), 219-233. doi: 10.1080/13803390802317542

119. Tsunoda, K., Yamane, Y., Nishizaki, M., & Tanifuji, M. (2001). Complex objects are represented in macaque inferotemporal cortex by the combination of feature columns. *Nature Neuroscience, 4*(8), 832-838. doi: 10.1038/90547

120. Uc, E.Y., Rizzo, M., Anderson, S.W., Qian, S., Rodnitzky, R.L., & Dawson, J.D. (2005). Visual dysfunction in Parkinson's disease without demetia. *Neurology, 65*(12), 1907-1913. doi: 10.1212/01.wnl.0000191565.11065.11

121. Urwyler, P., Nef, T., Killen, A., Collerton, D., Thomas, A., Burn, D., McKeith, I., & Mosimann, U.P. (2014). Visual complaints and visual hallucinations in Parkinson's disease. *Parkinsonism and Related Disorders, 20*(3), 318-322. doi: 10.1016/j.parkreldis.2013.12.009

122. Vidyasagar, T.R., & Eysel, U.T. (2015). Origins of feature selectivities and maps in the mammalian primary visual cortex. *Trends in Neurosciences, 38*(8), 475-285. doi: 10.1016/j.tins.2015.06.003

123. Villardita, C., Smirni, P., & Zappalá, (1983). Visual neglect in Parkinson's disease. *Archives of Neurology, 40*(12), 737-739. doi: 10.1001/archneur.1983.04050110055008

124. Vitay J., Hamker F.H. (2007) On the Role of Dopamine in Cognitive Vision. In: Paletta L., Rome E. (eds) Attention in Cognitive Systems. Theories and Systems from an Interdisciplinary Viewpoint. WAPCV 2007. Lecture Notes in Computer Science, vol 4840. Springer, Berlin, Heidelberg. doi: 10.1007/978-3-540-77343-6_23

125. Wagemans, J. (1997). Characteristics and models of human symmetry detection. *Trends in Cognitive Sciences, 1*(9), 346-352. doi: 10.1016/S1364-6613(97)01105-4

126. Warrington, E.K., & James, M. (1988). Visual apperceptive agnosia: A clinico-anatomical study of three cases. *Cortex, 24*(1), 13-32. doi: 10.1016/S0010-9452(88)80014-5

127. Weil, R.S., Schrag, A.E., Warren, J.D., Crutch, S.J., Lees, A.J., & Morris, H.R. (2016). Visual dysfunction in Parkinson's disease. *Brain, 139*(11), 2827-2843. doi: doi.org/10.1093/brain/aww175

128. Wilson, C.J., & Bevan, M.D. (2011). Intrinsic dynamics and synaptic inputs control the activity patterns of subthalamic nucleus neuron in health and in Parkinson's disease. *Neuroscience, 198*, 54-68. doi: 10.1016/j.neuroscience.2011.06.049.

129. Wu, T., Wang, L., Chen, Y., Zhao, C., Li, K., & Chan, P. (2009). Changes of functional connectivity in the motor network in the resting state in Parkinson's disease. *Neuroscience Letters, 460*(1), 6-10. doi: 10.1016/j.neulet.2009.05.046

130. Xu, Yaoda (2017). Reevaluating the sensory account of visual working memory storage. *Trends in Cognitive Science, 21*(10), 794-815. doi: 10.1016/j.tics.2017.06.013

131. Zacks, J.M. (2008). Neuroimaging studies of mental rotation: A meta-analysis and review. *Journal of Cognitive Neuroscience, 20*(1), 1-19. doi: 10.1162/jocn.2008.20013

132. Ziegler, W., Killan, B., & Deger, K. (1997). The role of the left mesial frontal cortex in fluent speech: Evidence from a case of left supplementary motor area hemorrhage. *Neuropsychologia, 35*(9), 1197-1208. doi: 10.1016/S0028-3932(97)00040-7

APPENDIX. IRB APPROVAL MEMO

IOWA STATE UNIVERSITY
OF SCIENCE AND TECHNOLOGY

Institutional Review Board
Office for Responsible Research
Vice President for Research
2420 Lincoln Way, Suite 202
Ames, Iowa 50014
515 294-4566

Date: 11/27/2017

To: Stephen J Anderson
W117 Lagomarcino

CC: Dr. Elizabeth L. Stegemoller
235 Forker

From: Office for Responsible Research

Title: Visual Processing in Parkinson's Disease

IRB ID: 16-381

Approval Date:	11/27/2017	**Date for Continuing Review:**	9/5/2018
Submission Type:	Modification	**Review Type:**	Full Committee

The project referenced above has received approval from the Institutional Review Board (IRB) at Iowa State University according to the dates shown above. Please refer to the IRB ID number shown above in all correspondence regarding this study.

To ensure compliance with federal regulations (45 CFR 46 & 21 CFR 56), please be sure to:

- **Use only the approved study materials** in your research, **including the recruitment materials and informed consent documents that have the IRB approval stamp.**
- **Retain signed informed consent documents for 3 years after the close of the study,** when documented consent is required.
- **Obtain IRB approval prior to implementing any changes** to the study by submitting a Modification Form for Non-Exempt Research or Amendment for Personnel Changes form, as necessary.
- **Immediately inform the IRB of (1) all serious and/or unexpected adverse experiences** involving risks to subjects or others; and (2) **any other unanticipated problems involving risks** to subjects or others.
- **Stop all research activity if IRB approval lapses,** unless continuation is necessary to prevent harm to research participants. Research activity can resume once IRB approval is reestablished.
- **Complete a new continuing review form** at least three to four weeks prior to the **date for continuing review** as noted above to provide sufficient time for the IRB to review and approve continuation of the study. We will send a courtesy reminder as this date approaches.

Please be aware that IRB approval means that you have met the requirements of federal regulations and ISU policies governing human subjects research. **Approval from other entities may also be needed.** For example, access to data from private records (e.g. student, medical, or employment records, etc.) that are protected by FERPA, HIPAA, or other confidentiality policies requires permission from the holders of those records. Similarly, for research conducted in institutions other than ISU (e.g., schools, other colleges or universities, medical facilities, companies, etc.), investigators must obtain permission from the institution(s) as required by their policies. **IRB approval in no way implies or guarantees that permission from these other entities will be granted.**

Upon completion of the project, please submit a Project Closure Form to the Office for Responsible Research, 202 Kingland, to officially close the project.

Please don't hesitate to contact us if you have questions or concerns at 515-294-4566 or IRB@iastate.edu.